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Vatinoxan – Medetomidine premedication during Cesarean section in dogs: effects on maternal hemodynamics and neonatal outcomes

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Abstract

Background

The use of alpha-2 adrenergic receptor agonists during canine cesarean section remains controversial because of their potential cardiovascular effects and influence on neonatal adaptation. Vatinoxan may attenuate the peripheral cardiovascular effects of medetomidine while preserving its anesthetic-sparing properties. This study evaluated the effects of medetomidine–vatinoxan premedication on maternal intraoperative physiological variables, anesthetic requirements, neonatal vitality, and umbilical cord blood parameters in bitches undergoing elective cesarean section.

Results

Thirty bitches were randomly assigned to receive either medetomidine–vatinoxan before propofol induction and isoflurane maintenance (MV+PROP, n = 15) or propofol–isoflurane anesthesia without premedication (PROP, n = 15). A total of 152 puppies were delivered. The MV+PROP group required a lower propofol dose for endotracheal intubation and lower intraoperative isoflurane concentrations. However, maternal heart rate was lower at skin incision and immediately after delivery of the last puppy, while systolic and mean arterial blood pressures were lower overall in this group. Hypotensive episodes were numerically more frequent in the MV+PROP group, although between-group differences were not statistically significant. Umbilical cord blood gas variables, electrolyte concentrations, glucose, and lactate did not differ significantly between groups. Apgar scores increased over time in both groups, but the improvement at 5 minutes was smaller in the MV+PROP group. No significant difference in Apgar scores was observed at 20 minutes. Twenty-four-hour neonatal survival was high and comparable between groups.

Conclusions

Medetomidine–vatinoxan premedication reduced propofol and isoflurane requirements but did not improve maternal hemodynamic stability or neonatal outcomes compared with propofol–isoflurane anesthesia alone. The transiently lower neonatal vitality at 5 minutes and lower maternal arterial blood pressure warrant caution. Further studies are needed to establish the clinical role and safety of this combination during canine cesarean section.

Background

Medetomidine, an alpha-2 adrenergic receptor agonist, is one of the most widely used sedative agents in veterinary medicine. Its sedative, analgesic, and muscle relaxant properties make it valuable for premedication before general anesthesia Medetomidine also reduces inhalational anesthetic requirements [1]. Despite these advantages, the administration of alpha-2 agonists is associated with

potential adverse effects, primarily mediated through stimulation of peripheral adrenergic receptors. Reported complications include bradycardia, arrhythmias, hypo- and hypertension, and decreased cardiac output [1–3].

Due to maternal side effects with potential fetal risk, alpha-2 agonists have long been discouraged in anesthetic protocols for cesarean section in small animals. Clinicians are concerned both about maternal cardiovascular disturbances, which may indirectly compromise fetal welfare, and about the direct depressive effects of alpha-2 agonists on the fetuses themselves. Of particular concern is the risk of severe bradycardia, as neonatal cardiac output depends almost entirely on heart rate, leaving neonates unable to compensate for a marked reduction [4]. This is particularly important during the transition from fetal to neonatal life, when cardiac development is not yet fully complete. Therefore, the use of alpha-2 agonists for cesarean sections (CSs) remains controversial. Moon et al. [5] reported an increased risk of stillbirth after premedication with xylazine. On the other hand, more recent studies have reported promising results. These studies have demonstrated satisfactory puppy survival and vitality following the administration of medetomidine [6] and dexmedetomidine [7, 8]. However, despite these encouraging findings, the use of alpha-2 agonists in anesthetic protocols for cesarean delivery is not recommended in clinical practice (WSAVA Pain Guidelines, 2024).This is likely due to the limited number of available studies and the well-known side effects associated with this class of drugs.

Vatinoxan (also known as MK-467 or L-659,066) is a peripheral antagonist of alpha-2 adrenergic receptors that crosses the blood–brain barrier only minimally. Therefore, the concomitant administration of medetomidine and vatinoxan allows preservation of the central sedative and analgesic effects of medetomidine, while potentially reducing its peripheral adverse vascular effects. This combination may improve cardiovascular stability by attenuating medetomidine-induced vasoconstriction without compromising sedation or analgesia. Beneficial effects of vatinoxan with alpha-2 agonists have been demonstrated in dogs, cats, and horses [9–11].

The addition of vatinoxan to medetomidine has been shown to increase heart rate, improve cardiac output, and reduce systemic vascular resistance, while attenuating significantly medetomidine-related side effects [12–14]. At the same time, the central sedative and analgesic effects of medetomidine are preserved ensuring adequate depth of sedation and pain control despite modulation of its peripheral actions [15, 16].

To date, there have been no published studies evaluated the effects of concurrent administration of vatinoxan and medetomidine within an anesthetic protocol for cesarean section. We hypothesize that the addition of vatinoxan to medetomidine may improve maternal cardiovascular stability and intraoperative physiological parameters during cesarean section. This effect may result from preservation of medetomidine-induced sedation and analgesia, potentially reducing anaesthetic requirements in a setting where opioid use is typically avoided prior to fetal removal, combined with peripheral α2-adrenoceptor blockade by vatinoxan, which may attenuate bradycardia and adverse

vascular responses, thereby supporting cardiac output and uterine perfusion in both the dam and the fetuses.

Therefore, the aim of this study was to evaluate maternal intraoperative physiological parameters, neonatal vitality, and umbilical cord blood gas variables following premedication with medetomidine–vatinoxan combined propofol induction and isoflurane maintenance, and to compare these outcomes with those obtained using a commonly applied anesthetic protocol for cesarean section in dogs, which omits premedication and relies on propofol induction and isoflurane maintenance alone.

Material and methods

Animals

Client-owned dogs undergoing elective cesarean section (CS) were enrolled after written owner consent. All bitches were clinically healthy based on physical examination, complete blood count, and serum biochemistry and were classified as ASA II. Dogs with systemic disease, pregnancy complications requiring emergency CS, or incomplete neonatal data were excluded from the study. The timing of CS was determined using serial progesterone measurements to estimate the luteinizing hormone (LH) surge, with surgery scheduled 63–64 days later. Pregnancy was monitored by weekly ultrasonography, and on day 63 post-LH surge, each bitch underwent clinical and ultrasonographic evaluation to determine whether CS should be performed immediately or postponed by 24 h. The decision to perform CS was based solely on clinical findings and was independent of treatment allocation.

Animal handling and study procedures were conducted in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Official Journal of the European Union L276/33, 2010). Ethical approval for the study procedures was obtained from the Animal Welfare Commission of the Wrocław University of Environmental and Life Sciences (Decision No. 8.2026). Written informed owner consent was obtained for all dogs. The target sample size of bitches was determined based on previous studies investigating anesthetic protocols and maternal and neonatal outcomes in dogs undergoing cesarean section [17–21].

Study design and anesthetic protocol

The study included 30 bitches. Before admission for surgery, dams were randomly allocated in a 1:1 ratio to one of two anaesthetic protocols by drawing one of 30 sealed opaque envelopes containing group assignments. In the MV+PROP group, dogs received intravenous medetomidine–vatinoxan before induction, whereas in the PROP group, an equal volume of physiological saline (0.9% NaCl) was administered as a placebo before the same induction and maintenance protocol. The anesthetist responsible for drug administration was aware of treatment allocation because of the nature of the interventions. However, personnel responsible for intraoperative monitoring data collection and neonatal Apgar score assessment were blinded to group allocation.

Approximately 15 minutes before the procedure, dams from both groups received subcutaneous injection of meloxicam (0.2 mg/kg SC; Metacam 5 mg/ml, Boehringer Ingelheim, Poland). After catheterization of the cephalic vein, females in the MV+PROP group received medetomidine with vatinoxan intravenously at doses of 0.005 mg/kg and 0.1 mg/kg, respectively (Zenalpha, Dechra Veterinary Products, Vetcare Finland), whereas dams in the PROP group received placebo. One minute later, dams in both groups were administered propofol (Propofol-Lipuro, 10 mg/ml; B. Braun Melsungen AG, Germany) intravenously at an initial dose of 3 mg/kg, with additional boluses administered as needed until an adequate depth of anesthesia for endotracheal intubation was achieved. Following endotracheal intubation, general anesthesia was maintained with isoflurane in oxygen (IsoVet, Piramal Healthcare, United Kingdom). After last puppy removal all dams received methadone intravenously (0.2 mg/kg, Comfortan, Eurovet Animal Health BV, Netherlands). Throughout anesthesia, all dams received intravenous fluids (Optilyte, Fresenius Kabi, Poland) at an initial rate of 5 ml/kg/h. Hypotension was defined as a mean arterial pressure below 60 mmHg [4]. In cases of hypotension, the first step was to reduce the concentration of the inhalational anesthetic, if feasible while maintaining an adequate depth of anesthesia. If hypotension persisted, the infusion rate was increased or an intravenous fluid bolus of 3–5 ml/kg was administered.

Anesthetic depth was evaluated continuously to ensure maintenance of an adequate and stable surgical plane. The appropriate anesthetic depth was defined by ventromedial rotation of the eyeball, absence of the palpebral reflex, decreased jaw tone, and stable heart and respiratory rates. The end-tidal isoflurane concentration was titrated accordingly using small incremental adjustments. Intraoperative nociception was inferred from deviations from baseline physiological variables, including heart rate (HR), respiratory rate (RR), and arterial blood pressure, as well as from the presence of reflex responses to surgical manipulation.

From induction to extubation, physiological variables were monitored continuously and recorded at 2-minute intervals using a Mindray ePM 12M Vet monitor. The following parameters were documented: electrocardiography (ECG), HR, RR, non-invasive systolic (SBP), mean (MBP), and diastolic (DBP) arterial blood pressure, peripheral hemoglobin oxygen saturation (SpO_2), end-tidal carbon dioxide concentration ($EtCO_2$), end-tidal isoflurane concentration (FeISO), and esophageal temperature (T). Non-invasive arterial blood pressure was measured using an oscillometric technique, with an appropriately sized cuff positioned on the forearm.

For intra- and intergroup comparisons, three predefined intraoperative time points were analysed: T1 – at skin incision; T2 – immediately after delivery of the last fetus; and T3 – at completion of surgery (end of skin closure). At each of the three time points, the recorded value was calculated as the mean of 2–3 consecutive measurements obtained at 2-minute intervals.

Surgical procedure

Cesarean section was performed via a standard ventral midline laparotomy. After exteriorization of the uterus, a longitudinal incision was made on the ventral or dorsal aspect of the uterine body, depending

on intraoperative conditions. Fetuses were delivered sequentially, and the uterine incision was closed with a continuous suture pattern using Monosyn® 3/0 (B. Braun Aesculap Chifa, Poland). The abdominal cavity was lavaged with warm sterile saline before routine closure of the abdominal wall, subcutaneous tissue, and skin using absorbable sutures.

Umbilical blood collection and blood gas analysis

Immediately after delivery and before placental separation, a mixed umbilical blood sample (≥ 100 µL) was collected into a heparinised syringe and analysed immediately using a handheld EpocVet blood gas analyser (Siemens Healthineers, Germany). Blood gas variables and electrolyte concentrations (Na^+, K^+, Cl^-, and ionised Ca^{2+}) were determined.

Newborns – obstetrical care and vitality evaluation

Initial neonatal care included airway clearance, drying, tactile stimulation, and routine umbilical cord management. All puppies were monitored for 7 days after delivery to assess survival and health status.

Neonatal viability was assessed by the same investigator using the modified canine Apgar score described by Veronesi et al. (2009). Assessments were performed immediately after delivery (before neonatal intervention) and at 5 and 20 min. Based on the total score, puppies were classified as normal (7–10), weak (4–6), or critical (0–3).

Newborn puppies presenting with congenital malformations were euthanized immediately after delivery. The procedure involved initial sedation with intramuscular dexmedetomidine (Dexdomitor, 0.05 mg/kg; Zoetis, Poland), followed by inhalation of isoflurane in oxygen administered via a face mask until loss of consciousness. Once unconsciousness had been achieved, pentobarbital (Euthasol, 400 mg/mL; Dechra, Poland) was administered intraperitoneally at a dose of 250 mg/kg.

Data analysis

Statistical analyses were performed using Jamovi (v. 2.6.44) and GraphPad Prism (v. 11.0.0). Data distribution was assessed using the Kolmogorov–Smirnov test with Lilliefors correction. General characteristics of the dams were compared using Student's t-test. Intraoperative variables were analysed using repeated-measures mixed-model ANOVA. Umbilical blood gas variables and Apgar scores were analysed using linear mixed-effects models with anesthetic protocol as a fixed effect and litter as a random effect. The incidence of hypotension was compared between groups at each time point using Fisher's exact test. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated as measures of effect size. Apgar score categories and 24-hour survival were compared using Fisher's exact test. Statistical significance was set at $P < 0.05$.

Results

Thirty bitches and 152 puppies were included in the study. Umbilical blood samples were successfully collected from 140 neonates, whereas mortality and survival analyses included all 152 puppies.

The demographic and procedural characteristics of the study population are presented in Table 1. Females in the MV+PROP group required a lower propofol dose for intubation (3.28 ± 0.70 vs. 4.65 ± 1.82 mg/kg; mean difference 1.37 mg/kg, 95% CI 0.33–2.41; p = 0.012).

Table 1
Baseline characteristics of the study population

Variable	MV+PROP	PROP
Age (years)	4.92 ± 2.18	4.43 ± 1.81
Body weight (kg)	20.30 ± 18.69	16.22 ± 11.64
Litter size	4.53 ± 2.55	5.13 ± 2.41
Duration of surgery (min)	56.78 ± 16.38	61.00 ± 11.97

Heart rate was significantly lower in the MV+PROP group at T1 and T2 (both p < 0.01), but not at T3. Mixed-model ANOVA demonstrated a significant time × protocol interaction (p < 0.0001; Fig. 1). Systolic blood pressure was lower in the MV+PROP group (group effect, p = 0.0016) and changed over time (time effect, p = 0.016), whereas no time × protocol interaction was observed. Mean arterial pressure showed a similar pattern, with lower values in the MV+PROP group (p = 0.04). Diastolic blood pressure changed over time only (p = 0.008). The proportion of dams experiencing hypotensive episodes did not differ significantly between anesthetic protocols at any analyzed time point. At T1, hypotension occurred in 40.0% of dams in the MV+PROP group and 13.3% in the PROP group (Fisher's exact test, p = 0.215). At T2 and T3, hypotensive episodes were observed in 66.7% of MV+PROP dams and 40.0% of PROP dams (p = 0.272 for both time points; Table 2).

Table 2
Incidence of hypotension at each intraoperative time point

Time point	Group	Hypotensive episodes, n (%)	Odds ratio (95% CI)	p-value
T1	MV+PROP	6 (40.0)	4.33 (0.7–26.0)	0.215
	PROP	2 (13.3)	reference	
T2	MV+PROP	10 (66.7)	3.00 (0.7–12.9)	0.272
	PROP	6 (40.0)	reference	
T3	MV+PROP	10 (66.7)	3.00 (0.7–12.9)	0.272
	PROP	6 (40.0)	reference	

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated with the PROP group as the reference category.

Isoflurane requirements were lower in the MV+PROP group (group effect, p = 0.005). $EtCO_2$ changed over time (p = 0.006), with no effect of protocol or interaction (Fig. 1).

No significant differences were observed between anesthetic protocols for any of the analyzed blood gas parameters, including pH, pCO_2, bicarbonate concentration, base excess, electrolytes, glucose, and lactate (all p > 0.05). These results remained consistent across all models after accounting for litter-related clustering (Table 3).

Table 3
Umbilical blood gas parameters and electrolyte concentrations in newborns from the MV+PROP and PROP groups.

	MV + PROP	**PROP**	**p value**
	(mean ± SD)		
pH (units)	7.14±0.12	7.15±0.08	0.77
pCO2 (mmHg)	73.70±21.23	72.08±16.56	0.75
cHCO3 (mmol/L)	27.76±29.05	24.95±3.53	1.00
BE (ecf) (mmol/L)	-4.87±4.00	-3.44±5.41	1.00
Na (mmol/L)	138.81±4.47	136.02±15.39	1.00
K (mmol/L)	4.07±0.76	4.15±0.77	1.00
Ca (mmol/L)	0.94±0.40	0.97±0.35	1.00
Cl (mmol/L)	110.52±4.54	110.30±5.19	1.00
BE (b) (mmol/L)	-6.59±3.10	-5.15±4.15	0.26
Glu (mg/dl)	71.16±21.18	81.29±24.69	0.16
Lac (mmol/L)	3.90±3.76	3.14±1.57	1.00

Apgar scores increased over time in both groups, with a significant protocol × time interaction (P = 0.007). Compared with the PROP group, puppies in the MV+PROP group showed a smaller increase in Apgar scores at 5 min (estimate − 0.83, 95% CI -1.35 to -0.31; p = 0.002), whereas no significant difference was observed at 20 min (estimate − 0.32, 95% CI -0.84 to 0.20; p = 0.231) (Fig. 2). The distribution of Apgar score categories differed between groups at 5 min (P < 0.01) and 20 min (p < 0.05; Table 4).

Table 4
Distribution of puppies classified as critical, weak, or normal in the MV+PROP and PROP groups at different time points.

Apgar scores	Group	0 min	5 min	20 min
		n (%)		
critical	MV+PROP	29 (42.7)	5 (7.3)	1 (1.5)
(0–3)	PROP	37 (44)	0 (0)	0 (0)
weak	MV+PROP	32 (47)	16 (23.5)	12 (17.6)
(4–6)	PROP	41 (48.2)	6 (7.2)	5 (5.9)
normal	MV+PROP	7 (10.3)	47 (69.2)	55 (81)
(7–10)	PROP	6 (7.2)	78 (92.8)	79 (94.1)

In total, 152 puppies were delivered via cesarean section: 68 in the MV+PROP group and 84 in the PROP group. Two neonates in the MV+PROP group and three in the PROP group presented with congenital malformations. At the owners' request, these puppies were euthanized immediately after delivery. One pup from the PROP group died 30 hours after cesarean section due to unknown causes. After excluding the five euthanized cases, the survival rate for the first 24 hours was 100% (66/66) in the MV+PROP group and 98.8% (80/81) in the PROP group. No significant difference in 24-hour survival rates was observed between the groups (Fisher's exact test, $p = 1.00$).

Discussion

To the authors' knowledge, the present study is the first to evaluate the combined use of medetomidine and vatinoxan in an anesthetic protocol for elective cesarean section in dogs, with particular emphasis on maternal hemodynamic stability and neonatal vitality. Achieving an adequate depth of anesthesia before fetal delivery remains challenging, as anesthetic protocols must ensure maternal safety while minimizing adverse effects on the offspring. Medetomidine, an α2-adrenoceptor agonist, reduces anesthetic requirements but may cause bradycardia, blood pressure disturbances, and decreased cardiac output, potentially compromising uteroplacental perfusion and fetal oxygenation. Vatinoxan, a peripherally acting α2-adrenoceptor antagonist, attenuates these cardiovascular effects while largely preserving sedation. We therefore hypothesized that combining medetomidine with vatinoxan would reduce anesthetic requirements while mitigating adverse maternal hemodynamic effects and potentially improving neonatal outcomes.

The principal finding was that premedication with medetomidine–vatinoxan provided a clear anesthetic-sparing effect, reflected by lower propofol requirements for endotracheal intubation and lower intraoperative isoflurane concentrations. However, these advantages were accompanied by lower maternal heart rate and arterial blood pressure and by a transiently less favorable neonatal response, as demonstrated by lower Apgar scores at 5 min. Importantly, the latter was not associated with detectable

alterations in umbilical blood gas, acid–base, electrolyte, glucose or lactate parameters, and the difference in Apgar scores was no longer significant at 20 min. Neonatal survival was similarly high with both protocols. Taken together, these findings suggest that the addition of medetomidine–vatinoxan improves anesthetic sparing but does not provide a clear overall advantage for cesarean section when maternal cardiovascular stability and early neonatal adaptation are considered simultaneously.

Vatinoxan, is a peripherally acting α2-adrenoceptor antagonist that attenuates the peripheral cardiovascular effects of alpha-2 agonists. Honkavaara et al. [12, 22] demonstrated that combining dexmedetomidine with vatinoxan reduced cardiovascular adverse effects compared with dexmedetomidine alone. Similarly, Salla et al [23] reported higher heart rates in dogs premedicated with medetomidine–vatinoxan before inhalational anesthesia. However, the effects of this combination during canine cesarean section remain unexplored. Based on these findings, we hypothesized that vatinoxan could mitigate the cardiovascular effects of medetomidine while preserving its sedative and anesthetic-sparing properties, thereby reducing inhalant anesthetic requirements and potentially benefiting both maternal and neonatal outcomes.

The potential benefits of this combination are particularly relevant during cesarean section, given the physiological adaptations associated with pregnancy and parturition. Pregnancy involves substantial cardiovascular, respiratory, and hormonal changes, while the increased metabolic demands and intra-abdominal pressure associated with the gravid uterus further influence maternal physiology. Surgical manipulation and exteriorization of the uterus may also affect maternal hemodynamics. The pronounced effects of alpha-2 adrenergic agonists on multiple physiological systems have been well documented across species, including dogs [1, 3, 24, 25]. However, their effects on maternal cardiovascular function during cesarean section remain scarce. Previous studies in dogs have primarily focused on neonatal outcomes, such as vitality and survival [6–8], with less attention given to maternal hemodynamic responses and their potential implications for fetal well-being.

Consistent with the above, our study showed that despite receiving less propofol and isoflurane, dams in MV+PROP group had lower heart rates during the earlier phases of anesthesia than those receiving propofol alone. Although HR values in both groups remained within acceptable limits and no episodes of bradycardia were observed, significant differences between groups at time points T1 and T2 in our study suggest that vatinoxan may not fully mitigate the cardiovascular effects of medetomidine. It has been demonstrated that intravenously administered medetomidine at a dose of 5 µg/kg maintains its cardiovascular effects for approximately 45–60 minutes [26], whereas the cardioprotective effects of vatinoxan develop rapidly after intravenous administration and persist for approximately 30–40 minutes [15]. Therefore, the absence of differences in HR between groups at T3 may be explained by the fact that, at this time point, the effects of both drugs had already largely subsided, with only residual effects remaining. This may have resulted in similar HR values between the groups at T3.

Differences between anesthetic protocols were observed not only in heart rate but also in arterial blood pressure. In present study SBP and MBP were significantly lower in the MV+PROP group, while DBP was

affected only by time. Hypotensive episodes were numerically more frequent in the MV+PROP group at all analyzed time points, with higher odds of hypotension compared with the PROP group (OR = 4.33 at T1 and OR = 3.0 at T2 and T3). Although these differences did not reach statistical significance, the consistently higher odds of hypotension suggest a potentially clinically relevant effect. The relatively small sample size (15 bitches per group) limited the statistical power to detect differences in hypotension frequency; therefore, the absence of statistical significance should not be interpreted as evidence of equivalent risk between protocols. Our findings are consistent with those of by Salla et al. [23], who reported moderate to marked hypotension in dogs premedicated with medetomidine combined with vatinoxan and subsequently anesthetized with sevoflurane. More recently, Rouse et al. [27] reported significantly lower mean arterial pressure and a greater need for hemodynamic interventions in dogs receiving medetomidine–vatinoxan compared with those premedicated with dexmedetomidine during inhalational anesthesia. Similarly, reduced arterial pressure following vatinoxan administration during inhalational anesthesia has been reported in other species [15, 28, 29]. This effect may be attributed to peripheral α2-adrenoceptor blockade, which attenuates medetomidine-induced vasoconstriction and reduces vascular resistance. The present findings suggest that this mechanism, combined with the vasodilatory effects of inhalational anesthesia, may contribute to maternal hypotension despite reduced anesthetic requirements.

The reduced propofol dose and lower inhalant anesthetic requirements observed in the MV+PROP group are consistent with the sedative and anesthetic-sparing properties of α2-adrenoceptor agonists. The anesthetic-sparing effect of medetomidine on both injectable and inhalant anesthetics has been well documented for many years [1]. Previous studies have shown that medetomidine can reduce the propofol dose required for induction by up to 75%, depending on the alpha-2 agonist dose used for premedication [30], and can decrease the minimum alveolar concentration (MAC) of isoflurane by 47.2% [31]. Although vatinoxan attenuates the anesthetic-sparing effect of medetomidine [32], this effect remained clearly evident in our study when compared with dams that did not receive premedication. Interestingly, reducing inhalant anesthetic requirements could theoretically improve cardiovascular stability, as isoflurane-induced cardiovascular depression is dose dependent. However, despite lower propofol and isoflurane requirements, bitches in the MV+PROP group exhibited lower arterial blood pressure than those in the PROP group. This finding may reflect attenuation of medetomidine-induced peripheral vasoconstriction by vatinoxan, potentially contributing to lower vascular resistance and arterial pressure.

Umbilical cord blood analysis complements clinical vitality assessment by providing information on fetal respiratory and metabolic status at delivery. Despite the maternal cardiovascular differences, no significant differences were found between the MV+PROP and PROP groups in umbilical blood pH, pCO_2, pO_2, bicarbonate, base excess, or lactate concentration, suggesting no detectable difference in fetal acid–base or metabolic status between the anesthetic protocols. The results obtained in the PROP group are consistent with those reported in our previous studies using similar anaesthetic protocols [17, 20, 21]. Although, reference ranges for umbilical cord blood gas parameters in canine neonates have not yet been established, the consistency with previous findings and the high neonatal survival rate suggest

that the recorded values may be compatible with physiological perinatal adaptation. Mild mixed acidosis was observed in both groups, which may reflect physiological acid–base changes associated with birth rather than a protocol-specific effect. This interpretation is also supported by findings in human neonates, in whom mild acidosis relative to adults has been reported following both vaginal delivery and cesarean section [33, 34]. Nevertheless, without established neonatal reference ranges, the physiological significance of these findings in puppies remains uncertain.

To the authors' best knowledge, this study is among the first to report electrolyte concentrations in canine umbilical cord blood. Electrolyte values did not differ between the two study groups. As with the previously discussed parameters, interpretation is limited by the lack of established reference values for umbilical cord blood in puppies. When compared with adult reference ranges, however, all neonates exhibited hypocalcemia, defined as ionized calcium below 1.2 mmol/L [35]. Similar findings were reported in our previous studies [17, 20] suggesting that these values may represent a physiological characteristics of neonatal dogs.

On the other hand, if the observed hypocalcemia were clinically relevant, typical signs such as stiff gait, behavioral changes, restlessness, excitation, aggression, hypersensitivity to stimuli, or disorientation would be expected [36]. However, such signs are difficult to assess in neonates and no abnormalities were reported by owners in the days following cesarean section. In human neonates, particularly those with low birth weight, decreased ionized calcium concentrations have also been reported [37]. Similarly, hypocalcemia noted in cases of newborn puppies may be associated with lower birth weight, which is more common in individuals born in large litters.

Interestingly, the absence of significant differences in umbilical cord blood parameters contrasted with the differences observed in neonatal Apgar scores. Puppies from MV+PROP dams showed a smaller improvement in Apgar scores at 5 min, although this difference was no longer significant at 20 min. This transient reduction in neonatal vitality may reflect delayed early postnatal adaptation, potentially associated with the sedative effects of medetomidine or the lower maternal arterial pressure observed in this group. Although data on the placental transfer of medetomidine–vatinoxan in dogs remain unavailable, previous studies have reported favourable neonatal outcomes following low-dose medetomidine [6] or dexmedetomidine administration [7, 8]. In contrast to these reports, puppies in the MV+PROP group in the present study showed significantly lower early Apgar scores than those receiving propofol alone, suggesting a transient adverse effect on neonatal vitality, potentially related to the sedative effects of medetomidine, despite the addition of vatinoxan. Although no corresponding differences in umbilical blood gas or metabolic parameters were detected, the relative contributions of drug exposure and maternal hemodynamic changes to this transient effect remain uncertain.

Our findings provide a different perspective on the maternal and neonatal effects of α2-adrenoceptor agonists during canine cesarean section compared with those reported in previous studies. To the best of the authors' knowledge, only one study has evaluated puppy vitality and survival after cesarean section using a protocol that included medetomidine premedication, propofol induction, and sevoflurane

maintenance. However, in that study, neonatal evaluation using the Apgar score was performed 15 minutes after delivery and after sublingual atipamezole administration [6]. Further it did not include vatinoxan, which was expected to mitigate the adverse cardiovascular effects of medetomidine. These methodological differences strongly limit direct comparison and, consequently, the strength of any discussion based on these data. We observed that effects potentially associated with medetomidine were still evident in both maternal hemodynamics and neonatal vitality, raising questions about the extent to which vatinoxan can counteract these effects.

Direct comparisons of neonatal Apgar scores between studies are limited by differences in anesthetic protocols, scoring systems, and assessment procedures. Unlike previous studies using medetomidine or dexmedetomidine without vatinoxan, the present study evaluated medetomidine combined with vatinoxan. An important methodological difference also concerns the timing of neonatal assessment and the use of postnatal interventions. In our study, the first Apgar score was recorded immediately after placental separation, before any neonatal resuscitation, and without prior administration of atipamezole. In contrast, De Cramer et al. [6] assessed neonatal vitality following atipamezole administration and at 15 min, whereas Groppetti et al. [7] and Di Cesare et al. [8] evaluated Apgar scores within 5 min after initial neonatal assistance. These methodological differences substantially limit direct comparisons. Assessment immediately after birth, before any intervention, may better reflect the puppies' initial clinical condition, although it does not allow the specific effects of medetomidine to be distinguished from those of other components of the anesthetic protocol.

Despite these limitations, comparison of Apgar scores obtained at 5 min after neonatal assistance may provide additional insight into early neonatal vitality across studies. In the present study, 92.3% of puppies in the PROP group and 68.8% in the MV+PROP group were classified as having normal vitality at 5 min after birth. For comparison, Groppetti et al. [7] reported normal vitality in 77.8% of puppies following dexmedetomidine–propofol anesthesia, while Di Cesare et al. [8] reported 88.2% following dexmedetomidine–alfaxalone anesthesia, both assessed at 5 min of life and after neonatal resuscitation. Although these percentages are not directly comparable, it is noteworthy that the proportion of puppies with normal vitality was lower in all groups exposed to medetomidine or dexmedetomidine than in our PROP group. These observations may suggest a potential influence of α2-adrenoceptor agonists on early neonatal vitality, although their specific contribution cannot be determined from these comparisons.

Conclusion

In summary, medetomidine–vatinoxan premedication produced a substantial propofol- and isoflurane-sparing effect in bitches undergoing cesarean section. The approximately 30% reduction in propofol dose could be considered advantageous, as propofol crosses the placenta, and excessive or repeated administration may contribute to neonatal cardiorespiratory depression. However, despite these anesthetic-sparing effects, the MV+PROP protocol was associated with lower maternal heart rate and arterial blood pressure and, contrary to expectations, transiently reduced neonatal vitality at 5 min after

birth. Although umbilical cord blood gas parameters and neonatal survival rates were comparable between groups, the addition of medetomidine–vatinoxan did not demonstrate a clear clinical advantage over propofol alone. Therefore, based on the present findings, routine use of this combination for elective canine cesarean section cannot be recommended. If administered, careful monitoring of maternal blood pressure and preparedness for neonatal resuscitation are essential

Abbreviations

ASA
American Society of Anesthesiologists
BE (b)
base excess in blood
BE (ecf)
base excess in extracellular fluid
Ca
ionized calcium
$cHCO_3$
bicarbonate concentration
CI
confidence interval
Cl
chloride
CS
cesarean section
DBP
diastolic blood pressure
ECG
electrocardiography
$EtCO_2$
end–tidal carbon dioxide concentration
FeISO
end–tidal isoflurane concentration
Glu
glucose
HR
heart rate
K
potassium
Lac
lactate

LH
luteinizing hormone
MBP
mean arterial blood pressure
MV+PROP
group receiving medetomidine and vatinoxan prior to propofol induction
Na
sodium
OR
odds ratio
pCO_2
partial pressure of carbon dioxide
pH
potential of hydrogen
PROP
control group receiving placebo prior to propofol induction
RR
respiratory rate
SBP
systolic blood pressure
SpO_2
peripheral oxygen saturation
T
esophageal temperature.

Declarations

Ethics approval and consent to participate:

Ethical approval for the study procedures was obtained from the Animal Welfare Commission of the Wrocław University of Environmental and Life Sciences (Decision No. 8.2026). Written informed owner consent was obtained for all dogs.

Consent for publication:

Not applicable

Competing interests:

The authors declare that they have no competing interests

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Author Contribution

MO –conceptualisation, data collection, data evaluation, reviewing and editing the paper; HT - neonatal data collection and analysis, editing the paper; AM - patient monitoring, collection and analysis of maternal vital signs data, editing the paper; AA – conceptualisation, data collection, data evaluation and statistical analysis, writing of the manuscript;

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Not applicable

Data Availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

References

1. Sinclair MD. A review of the physiological effects of alpha2-agonists related to the clinical use of medetomidine in small animal practice. Can Vet J. 2003;44:885–97.
2. Pypendop BH, Verstegen JP. Hemodynamic effects of medetomidine in the dog: a dose titration study. Vet Surg. 1998;27:612–22. https://doi.org/10.1111/j.1532-950x.1998.tb00539.x.
3. Paddleford RR, Harvey RC. Alpha 2 agonists and antagonists. Vet Clin North Am Small Anim Pract. 1999;29:737–45. https://doi.org/10.1016/s0195-5616(99)50058-2.
4. Grimm KA, Lamont LA, Tranquilli WJ, Greene SA, Robertson SA. Veterinary anesthesia and analgesia: The fifth edition of Lumb and Jones. Wiley; 2015.
5. Moon PF, Erb HN, Ludders JW, Gleed RD, Pascoe PJ. Perioperative risk factors for puppies delivered by cesarean section in the United States and Canada. J Am Anim Hosp Assoc. 2000;36:359–68.
6. De Cramer KGM, Joubert KE, Nöthling JO. Puppy survival and vigor associated with the use of low dose medetomidine premedication, propofol induction and maintenance of anesthesia using sevoflurane gas-inhalation for cesarean section in the bitch. Theriogenology. 2017;96:10–5.

7. Groppetti D, Di Cesare F, Pecile A, Cagnardi P, Merlanti R, D'Urso ES, et al. Maternal and neonatal wellbeing during elective C-section induced with a combination of propofol and dexmedetomidine: How effective is the placental barrier in. dogs? Theriogenology. 2019;129:90–8. https://doi.org/10.1016/j.theriogenology.2019.02.019.
8. Di Cesare F, Brioschi FA, Ravasio G, Groppetti D, Amari M, Giussani E, et al. Dexmedetomidine and alfaxalone intravenous co-administration for the induction of general anaesthesia in bitches undergoing C-section: impact on newborn viability and pharmacokinetics. Theriogenology. 2025;247:117578. https://doi.org/10.1016/j.theriogenology.2025.117578.
9. Rolfe NG, Kerr CL, McDonell WN. Cardiopulmonary and sedative effects of the peripheral α2-adrenoceptor antagonist MK 0467 administered intravenously or intramuscularly concurrently with medetomidine in dogs. Am J Vet Res. 2012;73:587–94. https://doi.org/10.2460/ajvr.73.5.587.
10. Vainionpää M, Salla K, Restitutti F, Raekallio M, Junnila J, Snellman M, et al. Thermographic imaging of superficial temperature in dogs sedated with medetomidine and butorphanol with and without MK-467 (L-659'066). Vet Anaesth Analg. 2013;40:142–8. https://doi.org/10.1111/j.1467-2995.2012.00768.x.
11. Pypendop BH, Honkavaara J, Ilkiw JE. Cardiovascular effects of dexmedetomidine, with or without MK-467, following intravenous administration in cats. Vet Anaesth Analg. 2017;44:52–62. https://doi.org/10.1111/vaa.12397.
12. Honkavaara JM, Restitutti F, Raekallio MR, Kuusela EK, Vainio OM. The effects of increasing doses of MK-467, a peripheral alpha(2)-adrenergic receptor antagonist, on the cardiopulmonary effects of intravenous dexmedetomidine in conscious dogs. J Vet Pharmacol Ther. 2011;34:332–7. https://doi.org/10.1111/j.1365-2885.2010.01242.x.
13. Joerger FB, Wieser ML, Steblaj B, Niemann L, Turunen H, Kutter APN. Evaluation of cardiovascular effects of intramuscular medetomidine and a medetomidine–vatinoxan combination in Beagle dogs: A randomized blinded crossover laboratory study. Veterinary Anaesth Analg. 2023;50:397–407. https://doi.org/10.1016/j.vaa.2023.05.004.
14. Restitutti F, Kaartinen MJ, Raekallio MR, Wejberg O, Mikkola E, del Castillo JRE, et al. Plasma concentration and cardiovascular effects of intramuscular medetomidine combined with three doses of the peripheral alpha2-antagonist MK-467 in dogs. Veterinary Anaesth Analg. 2017;44:417–26. https://doi.org/10.1016/j.vaa.2016.04.006.
15. Salla K, Restitutti F, Vainionpää M, Junnila J, Honkavaara J, Kuusela E, et al. The cardiopulmonary effects of a peripheral alpha-2-adrenoceptor antagonist, MK-467, in dogs sedated with a combination of medetomidine and butorphanol. Veterinary Anaesth Analg. 2014;41:567–74. https://doi.org/10.1111/vaa.12158.
16. Bellini L, Zanusso F, Lucatello L, Dussin B, Capolongo F. Comparison of premedication with or without vatinoxan, co-administered with medetomidine and methadone, in anesthetized dogs. Res Vet Sci. 2025;197:105958. https://doi.org/10.1016/j.rvsc.2025.105958.

17. Antończyk A, Ochota M, Niżański W. Umbilical Cord Blood Gas Parameters and Apgar Scoring in Assessment of New-Born Dogs Delivered by Cesarean Section. Anim (Basel). 2021;11:685. https://doi.org/10.3390/ani11030685.
18. Antończyk A, Kiełbowicz Z, Niżański W, Ochota M. Preliminary study on fluid bolus administration for prevention of spinal hypotension in dogs undergoing elective cesarean section. Front Vet Sci. 2023;10:1112845. https://doi.org/10.3389/fvets.2023.1112845.
19. Antończyk A, Kiełbowicz Z, Niżański W, Ochota M. Comparison of 2 anesthetic protocols and surgical timing during cesarean section on neonatal vitality and umbilical cord blood parameters. BMC Vet Res. 2023;19:48. https://doi.org/10.1186/s12917-023-03607-2.
20. Antończyk A, Ligocka- Kowalczyk Z, Ochota M. Choosing wisely: Effects of propofol and alfaxalone induction on maternal and neonatal outcomes in isoflurane-anesthetized dogs undergoing cesarean section. Vet J. 2026;317:106618. https://doi.org/10.1016/j.tvjl.2026.106618.
21. Antończyk A, Ochota M. Is an epidural component during general anaesthesia for caesarean section beneficial for neonatal puppies'. health vitality? Theriogenology. 2022;187:1–8. https://doi.org/10.1016/j.theriogenology.2022.04.015.
22. Honkavaara JM, Raekallio MR, Kuusela EK, Hyvärinen EA, Vainio OM. The effects of L-659,066, a peripheral α2-adrenoceptor antagonist, on dexmedetomidine-induced sedation and bradycardia in dogs. Veterinary Anaesth Analg. 2008;35:409–13. https://doi.org/10.1111/j.1467-2995.2008.00403.x.
23. Salla KM, Turunen HA, Kallio-Kujala IJ, Pekkola V, Casoni DC, Lepajoe J, et al. Effects of vatinoxan in dogs premedicated with medetomidine and butorphanol followed by sevoflurane anaesthesia: a randomized clinical study. Veterinary Anaesth Analg. 2022;49:563–71. https://doi.org/10.1016/j.vaa.2022.08.002.
24. Lemke KA. Perioperative use of selective alpha-2 agonists and antagonists in small animals. Can Vet J. 2004;45:475–80.
25. Enouri SS, Kerr CL, McDonell WN, O'Sullivan ML, Neto FJT. Effects of a peripheral α2 adrenergic-receptor antagonist on the hemodynamic changes induced by medetomidine administration in conscious dogs 2008. https://doi.org/10.2460/ajvr.69.6.728
26. Pypendop BH, Verstegen JP. Hemodynamic Effects of Medetomidine in the Dog: A Dose Titration Study. Vet Surg. 1998;27:612–22. https://doi.org/10.1111/j.1532-950X.1998.tb00539.x.
27. Rouse S, Muñoz K, Lerche P, Ballash G, Midon M, Aarnes TK, et al. Medetomidine-vatinoxan is associated with a higher proportion of hypotension than dexmedetomidine in anesthetized dogs: a retrospective, matched-cohort study. Am J Vet Res. 2026;1:1–9. https://doi.org/10.2460/ajvr.26.08.0372.
28. Jaeger AT, Pypendop BH, Ahokoivu H, Honkavaara J. Cardiopulmonary effects of dexmedetomidine, with and without vatinoxan, in isoflurane-anesthetized cats. Vet Anaesth Analg. 2019;46:753–64. https://doi.org/10.1016/j.vaa.2019.05.012.

29. Vainionpää MH, Raekallio MR, Pakkanen SAE, Ranta-Panula V, Rinne VM, Scheinin M, et al. Plasma drug concentrations and clinical effects of a peripheral alpha-2-adrenoceptor antagonist, MK-467, in horses sedated with detomidine. Vet Anaesth Analg. 2013;40:257–64. https://doi.org/10.1111/vaa.12012.
30. Hammond RA, England GCW. The effect of medetomidine premedication upon propofol induction and infusion anaesthesia in the dog. J Veterinary Anaesth. 1994;21:24–8. https://doi.org/10.1111/j.1467-2995.1994.tb00478.x.
31. Ewing KK, Mohammed HO, Scarlett JM, Short CE. Reduction of isoflurane anesthetic requirement by medetomidine and its restoration by atipamezole in dogs. Am J Vet Res. 1993;54:294–9.
32. Hector RC, Rezende ML, Mama KR, Steffey EP, Raekallio MR, Vainio OM. Combined effects of dexmedetomidine and vatinoxan infusions on minimum alveolar concentration and cardiopulmonary function in sevoflurane-anesthetized dogs. Veterinary Anaesth Analg. 2021;48:314–23. https://doi.org/10.1016/j.vaa.2020.12.007.
33. Saneh H, Mendez MD, Srinivasan VN. Cord Blood Gas. Treasure Island (FL): StatPearls Publishing;: StatPearls; 2025.
34. Higgins C. Umbilical-cord blood gas analysis. Article from: Acutecaretesting Org; 2014.
35. de Brito Galvão JF, Schenck PA, Chew DJ. A Quick Reference on Hypercalcemia. Veterinary Clinics of North America. Small Anim Pract. 2017;47:241–8. https://doi.org/10.1016/j.cvsm.2016.10.016.
36. Silverstein DC, Hopper K. Small Animal Critical Care Medicine. W.B. Saunders; 2023. https://doi.org/10.1016/C2017-0-04165-4.
37. Root A, Diamond F. Disorders of Mineral Homeostasis in the Newborn, Infant, Child, and Adolescent. Pediatric Endocrinology, 2008, pp. 686–769. https://doi.org/10.1016/B978-141604090-3.50022-3

Figures

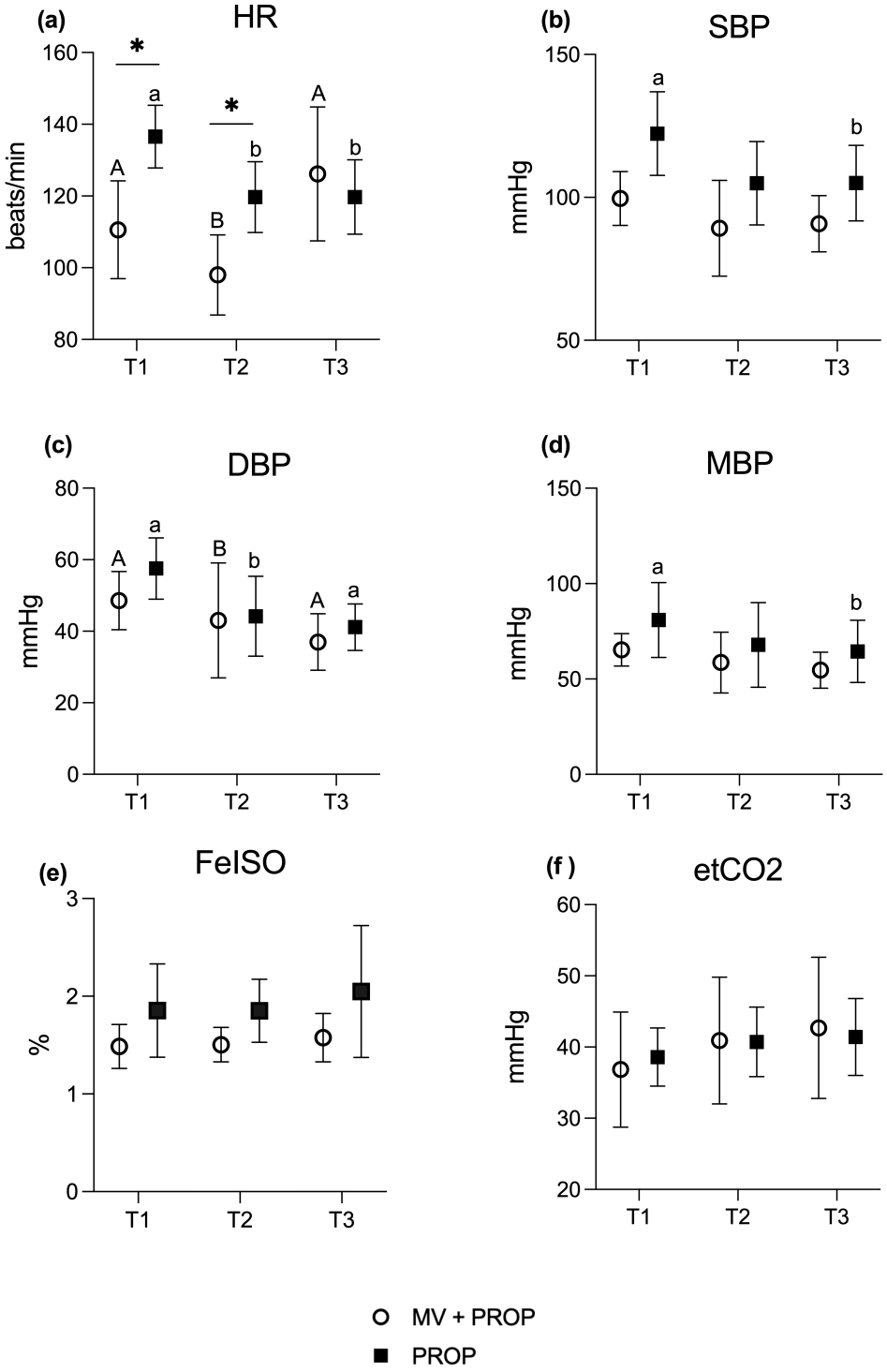

Figure 1

Mean with 95% CI of vital parameters over time in females anesthetized with MV+PROP and PROP.

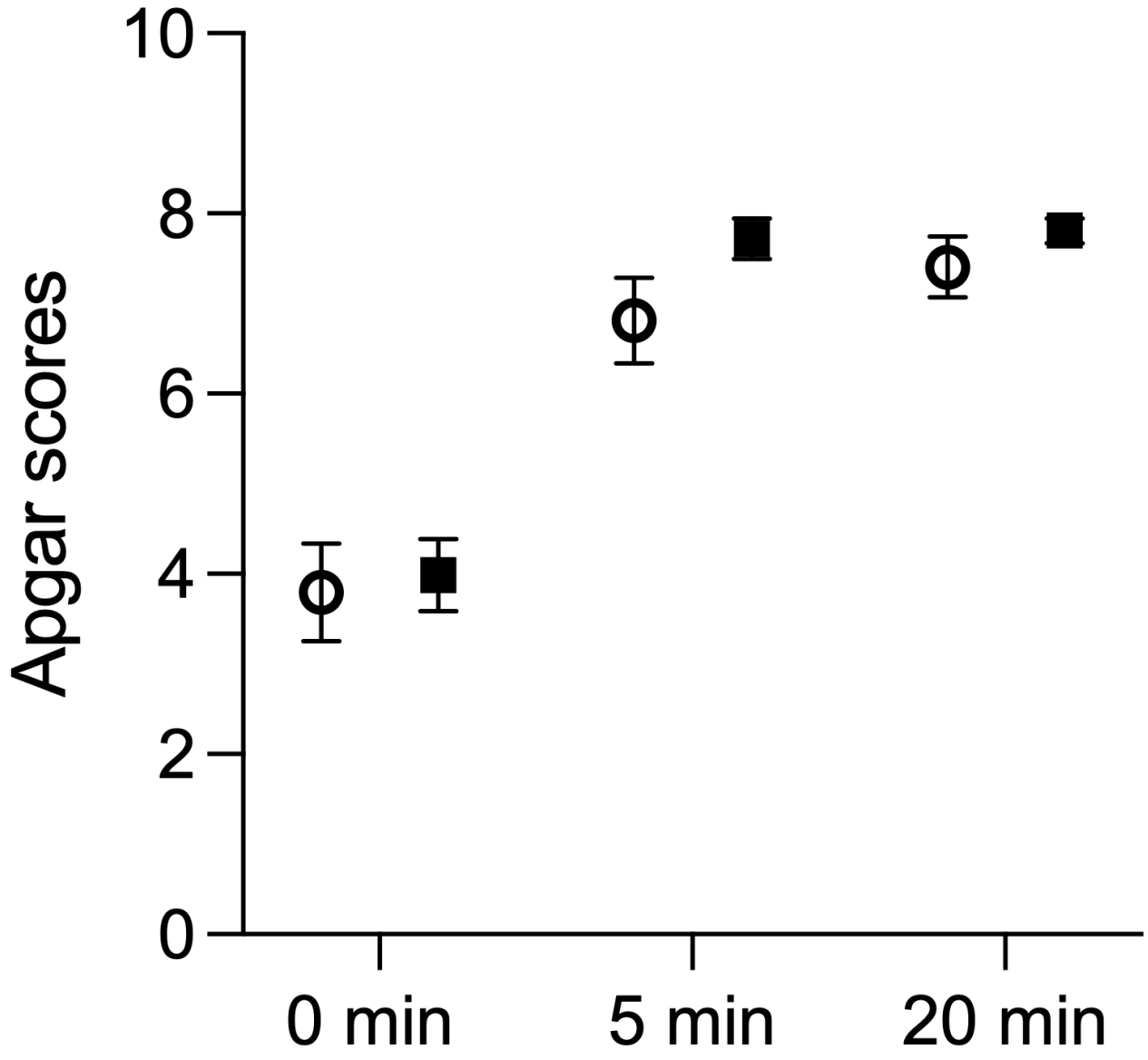

Figure 2

Apgar scores of newborns from the MV+PROP and PROP groups at 0, 5, and 20 minutes after delivery