



Neonatal severity indicators in dogs

Indicadores de severidade neonatal em cães

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Abstract

Despite the increasing interest for canine neonatology many aspects of canine neonatology are still not completely studied and perinatal mortality rates are high.

The identification of newborn puppies at high risk at birth/hospitalization is the main goal in advancing veterinary neonatology, as well as the improvement of newborn assessment protocols. The identification of at risk puppies should rely on objective indicators of severity, allowing a differentiated clinical assistance according to neonatal conditions and allowing canine perinatal mortality reduce.

This paper presents and discuss the neonatal severity indicators presently useful in the dog, as demonstrated by the specific scientific literature. Among them, some can be used only at birth, others only during the subsequent neonatal period and some useful at both times. Despite the availability of some useful severity indicators, the development of severity score systems are considered necessary also in dogs as in humans.

keywords: dog, newborn, severity indicators, outcome

Introduction

Although the increasing recent interests for canine neonatology, many aspects of canine neonatology are still not completely studied and perinatal mortality rates are high.

The identification of newborn puppies at high risk of developing adverse outcomes at birth/hospitalization is the main goal in advancing veterinary neonatology, as well as the improvement of newborn assessment protocols. The identification of at risk puppies should rely on objective indicators of severity, allowing a differentiated clinical assistance according to neonatal conditions.

Neonatal adaptation

In mammals, the process of birth is characterized by the quick transition from the well-protected intrauterine to the harmful extrauterine environment. Neonatal survival depends on a multisystemic complex process of physiological changes known as “neonatal adaptation”. Neonatal adaptation is fast and efficient in species such as horse and bovine, but slower and less efficient in altricial species, such as the dog. Moreover, in the dog, multiple neonates are delivered at a single parturition, with consequent longer expulsion phase in comparison to species delivering single neonates. Dystocia, can also occur rather frequently in some dog breeds, increasing the possible disturbance to the process of neonatal adaptation. Taking together the above mentioned characteristics, the dog neonate shows vulnerability not only at the time of birth, but also along the entire neonatal period, considered as the time between birth and the 3rd-4th week of age, and concur to explain the high perinatal losses in this species.

Perinatal mortality, definition, numbers and predisponente factors

Perinatal mortality, is considered as the sum of stillbirth plus neonatal losses, occurring the first 3 weeks of age. In dogs perinatal mortality was reported to reach high value, up to 20-40%, including 11% stillbirth and 8-31% of neonatal death (Gill, 2001; Indrebø et al., 2007; Tønnessen et al., 2012; Mila et al., 2014; Münnich and Küchenmeister, 2014; Mila et al., 2017). Neonatal deaths accounts 3% of death <24 h (Mila et al., 2017), 17-21% between 1 and 21 days (Mila et al., 2015; Mila et al., 2017), 35-36% in the first 2 days (Mila et al., 2015; Mugner et al., 2020) and 29-67% <7 days.

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Many factors can affect perinatal mortality in the dog. Among them, factors related to the process of birth (type of delivery, length, order of birth, litter-size); puppy's factors (maturity, viability, birth weight, malformations, immunity); maternal factors (breed, age, parity, diseases, cares, lactation); environmental factors (temperature, humidity, hygiene, ventilation, disturbances) and infections (bacteria, viruses, parasites).

The newborn dog as a patient

Veterinarians can be asked to manage newborn puppies also as patients. This represents a real challenge for the vet because of the peculiar characteristics of the newborn dog, such as the small size, the metabolic instability, the quick changes general status, the short interval symptoms-death, the unspecific symptoms, the weak reactivity, the high water turn-over, the high predisposition to dehydration and the difficult of performing complete or repeated blood analysis.

Therefore, the newborn dog is recognized as highly vulnerable and as a difficult patient, but, the vet has the need to reduce the perinatal mortality rate. This could only be achieved thanks a full knowledge of neonatal physiology, pathophysiology, diagnostic, pharmacology, and therapy, but especially thanks to the availability of severity indicators allowing the prompt recognition of at risk puppy, to differentiate the clinical approach to the newborns and, in turn, to improve neonatal survival.

Severity score systems in humans and common severity indicators

In humans, the early warning scores for neonatal mortality but also for predicting morbidity/illness severity has been widely recognized as pivotal. Therefore, many severity score systems have been developed in the last decades. Most of these systems have been designed on the basis of data obtained by the Apgar evaluation, the clinical examination and the blood screening. Among the parameters identified as severity indicators, birth weight, gestational age, body temperature, and apgar score are recurrent and common o many severity systems.

Severity indicators in dogs at birth and neonatal period

To the author knowledge, at present no severity systems have been proposed for the newborn dog. However, some severity indicators have been identified. Some of them are useful only at birth, others only during the subsequent neonatal period, and some could be useful both at birth and in the neonatal period.

At birth severity indicators include: blood gas analysis/lactatemia, Apgar score, birth weight, hypoglycaemia, hypothermia, severe malformations, placental necrosis. In the neonatal period severity indicators include: weight gain, hypothermia, hypoglycaemia, dehydration, failure immune transfer.

Asphyxia

The transition from intra- to extra-uterine life accompanied by varying degrees of hypoxia, generally well tolerated by newborns (Singer, 1999). In the dog, newborns were reported to suffer at birth of physiologic mild, transitory metabolic acidosis (Lucio et al., 2009; Mila et al., 2017). However, the prolonged hypoxia leads to metabolic acidosis, a harmful condition for the neonate because of $>pCO_2$ (respiratory acidosis), accumulation of acid radicals (metabolic acidosis), glucose depletion (hypoglycaemia) and bradycardia.

In humans, intrapartum asphyxia in babies account for 7–15% of neonatal mortality and severe morbidity, presently limited to 4-5%. Asphyxia causes an increased risk of long-term morbidity, and some authors reported that neonatal acidosis is associated to poor Apgar score in babies (Bobrow and Soothill, 1999; Omo-Aghoja, 2014). In dogs, mixed acidosis was reported to be a cause of poor neonatal performance (Lucio et al., 2009; Vassalo et al., 2015).

Asphyxia can be assessed by blood gas analysis, that traditionally includes the following parameters: pH, pCO_2 , pO_2 , HCO_3^- , BE, sO_2 , ions, glucose, lactate, PCV, Hb.

The most important parameters are pH and lactate. However, it should be noted that pH indicates the degree of acidosis but not the aetiology. The importance of pH assessment in the dog was reported by some authors. It was indeed reported that pH is an accurate predictor of neonatal outcome in dogs (Westgren et al., 1995), that pH and BE high prognostic value adverse neonatal outcome and that pH, BE,



and lactate represent predictors of neonatal morbidity (Vanspranghels et al., 2020). According to Crissiuma et al., 2006 and Lucio et al., 2009, pH is associated with clinical evaluation, and CO₂ and bicarbonate with the clinical prognosis of the neonate after birth. Blood lactate is important for assessing the clinical conditions of the patient and for the newborn survival prognosis. Oliva et al. (2018) reported that blood lactate is an indicator of neonatal distress as correlated with Apgar score in puppies born by CS. Umbilical vein lactate was found to be useful to undertake resuscitation or medical treatment and ensure a better neonatal survivability (Kuttan et al., 2016).

When blood lactate as a severity indicator is concerned, a study by Mila et al. (2017), in which venous blood lactate measured <8 h and at Day 1 was not associated to neonatal death at 1-21 d of age. On the opposite, other studies demonstrated the usefulness of this parameter as a prognostic factor, although with different thresholds. Kuttan et al., 2016 reported that 13 mmol/L umbilical lactate concentrations in puppies were found in puppies that died within 24 of age. Castagnetti et al. (2017), suggested that blood lactate concentrations of 10 vs 6.7 mmol/L in puppies dying within the first day of life. In previous studies, Groppetti et al. (2010), suggested the value of 5 mmol/L umbilical venous lactate cut-off as prognostic value in puppies, whilst Vivan et al. (2009) found an association between blood lactate >8 mmol/L and puppies' death or neurological complications. Only one study assessed the association between amniotic lactate concentrations and newborn puppy survival at 24 h after birth, but no differences were found between surviving and not surviving puppies (Bolis et al., 2018).

Viability

Viability is considered as the physiologic condition and reactivity of a neonate that influence the chance of surviving. A newborn puppy is considered as viable when it breaths efficiently soon after birth, crys clear, crawls toward maternal body, searches for the mammary gland, grasps the nipple, suck efficiently and shows normal neonatal reflexes. Neonatal viability can be therefore assessed by the Apgar score, the evaluation of puppy's behavior and by puppy reflexes score.

Among them the Apgar score has been widely recognised from long time in humans, from decades in horses and from about ten years also in the dog. The strenghtness of the Apgar score are the ability to provide a classification of newborn distress allowing a more accurate neonatal assistance on one side, and as prognostic factor for the first 24-48 h survival. In the dog, the usefulness of the Apgar score systems for canine newborns was tested by many studies (Veronesi et al., 2009; Groppetti et al., 2010; Doebeli et al., 2013; Batista et al., 2014; Vassalo et al., 2015; Veronesi, 2016; Bolis et al., 2017; Mila et al., 2017; Titkova et al., 2017; Veronesi et al., 2018; Vilar et al., 2018; Ballotta et al., 2019; Fusi et al., 2020; Tesi et al., 2020; Antonczyk et al., 2021). Moreover, the importance of the Apgar score as a short-term prognostic factor was proved by some authors (Veronesi et al., 2009; Doebeli et al., 2013; Batista et al., 2014; Veronesi, 2016; Mila et al., 2017; Vilar et al., 2018; Fusi et al., 2020; Antonczyk et al., 2021). However, the study differed for the cut-off value to discern between normal viable and less viable puppies, reported to be the value of 7 (Veronesi et al., 2009; Doebeli et al., 2013; Veronesi, 2016; Bolis et al., 2017; Mila et al., 2017; Veronesi et al., 2018; Vilar et al., 2018; Antonczyk et al., 2021), 6 (Vassalo et al., 2015) or 5 (Batista et al., 2014). Within the less viable class, 0-3 scored puppies were considered severely distressed, 4-6 moderately distressed, and < 5 newborns with reduced vitality (Vilar et al., 2018).

When newborns outcome at 24 h of age (alive/dead) is assessed according to the viability classes, it was found that puppies scored 7-10 show 95-100% survival (Veronesi et al., 2009; Bolis et al., 2017; Titkova et al., 2017; Bolis et al., 2018; Veronesi et al., 2018; Vilar et al., 2018; Fusi et al., 2020); puppies scored 4-6 show 94-100% survival (Titkova et al., 2017; Vilar et al., 2018; Fusi et al., 2020); puppies scored 0-3 show 0-39-100% survival (Veronesi, 2016; Bolis et al., 2017; Titkova et al., 2017; Veronesi et al., 2018; Vilar et al., 2018; Fusi et al., 2020). Therefore the best cut-off value for higher risk of death within 24h was suggested to be ≤ 3 (21% did not survive) (Antonczyk et al., 2021), while Apgar score cut-off 4 was proposed by Fusi et al. (2020), and cut-off 6 was reported to be the best predictor for neonatal survival by Mila et al. (2017).

Low birth weight and weight gain

Birthweight (BW) results from an adequate intrauterine environment, placental function and efficiency and fetal development and growth. It is influenced by maternal, placental and fetal counterparts and plays a pivotal role in the chance to survive of a newborn dog. Birthweight is a low cost and easy-to-evaluate parameter (Tesi et al., 2020). In the past breed-group cut-off value definition of BW were



reported, but more recently, breed-specific references were requested. Similarly to humans, also for the dog low birth weight (LBW) has been defined (Mugnier et al., 2019; Schrank et al., 2019; Fusi et al., 2020; Tesi et al., 2020; Fusi et al., 2021). Low birthweight newborns are characterised by lower energy reserves and stability, less viability, body temperature instability, metabolic failure/insufficiency/impairment, disadvantage in the nutritional competition with siblings. Low birthweight was found to be associated to neonatal mortality by some studies (Grundy, 2006; Indrebo et al., 2007; Groppetti et al., 2015; Mila et al., 2015; Mila et al., 2017; Fusi et al., 2021). Mila et al. (2015) reported that 81% of deaths within 2 days were associated with LBW. Therefore LBW was considered as a negative prognostic factor for diseases or mortality (Tonnessen et al., 2012; Mila et al., 2015; Cornelius et al., 2019; Mugnier et al., 2019; Tesi et al., 2020), especially in toy and small-sized breeds (Tonnessen et al., 2012).

However, on the basis of the importance, also for the dog, of identifying newborns with very low birth weight (VLBW), a study (Mugnier et al., 2020) reported first data about the definition of VLBW in puppies. The authors showed that 34% of deaths occurring within 2 days of age were associated with LBW, and that 48% of deaths were observed in puppies with VLBW (Mugnier et al., 2020). According to puppies BW, mortality at 1-21 days of age accounted for 4.2% in normal BW, 8.8% in LBW and 55.3% in VLBW newborns (Mugnier et al., 2020). Beside BW also weight gain (WG) is an accurate indicator of neonatal growth and well-being. After a physiologic 10% weight loss acceptable within the first 1-2 days, a steady WG should follow. Thus, also the constant monitoring of weight is important for detecting at risk puppies. However, also for WG, breed-specific cut-off growth rate are mandatory. According to the possible weight loss first stage, a study reported that >10% weight loss during the first 2-4 days of life may have a negative impact on neonatal survival (Bigliardi et al., 2013). Mila et al. (2012) reported that weight loss occurring between birth and Day 4 of age are associated to higher risk of death within the first 3 weeks. According to growth rate, low growth rate within the first 2 d of age represents a major risk factor for mortality during 2-21 days of age (Mila et al., 2015). Growth rate at or below -4% after the first 2 d of life were associated to 38% mortality (Mila et al., 2015), while the absence of weight gain was found in non surviving Dobermann puppies (Fusi et al., 2021).

Failure of immune transfer

Because of the endothelial placenta, puppies are nearly agammaglobulinemic at birth, with IgG blood concentration of 0.3 g/L at birth vs 8-25 g/L in adults. As a consequence immune efficiency relies on the passive immune transfer from the mother, by colostrum intake, that should occur in the first hours after birth (Chastant-Maillard et al., 2012). The failure of immune transfer predispose the puppy to a condition of vulnerability for infectious diseases. In a study from Mila et al. (2014), poor passive immune transfer was detected in 18% of neonates. The authors identified a threshold for IgG median serum concentrations at 2 days (230 mg/L) associated to <3-weeks mortality 44% vs 4.9% for puppies with IgG concentrations above that threshold (Mila et al., 2014). The IgG concentrations in puppies dead 2-21 days of age was indeed 172mg/dl (Mila et al., 2014). Moreover, IgG concentrations at 2 days of age resulted also associated to weight gain during the first 2 days (Mila et al., 2014).

Hypoglycaemia

The newborn dog is predisposed to hypoglycaemia because of its hepatic immaturity, limited energetic reserves, immature systems for glucose balance. In addition, also neonatal diseases/conditions, such as sepsis/endotoxemia, liver dysfunction, glycogen storage enzymatic abnormalities, low birth weight can lead to hypoglycaemia. Maternal diseases (starvation, placental abnormalities, gestational diabetes) can also be a cause for neonatal hypoglycaemia, as well as neonatal feeding disturbances, such as starvation, poor nursing, maternal agalactia. The risk of hypoglycaemia is counteracted by the regular assumption of energy by colostrum and milk intake and absorption, by the normal newborn metabolism, and by the condition of healthy and normal weighted newborn. Hypoglycaemia has been recognised as a main cause of neonatal mortality in dogs (Johnston et al., 2001; Lawler, 2008; Munnich and Kuchenmeister, 2014). After a first stage characterised by adrenergic symptoms, including shivering, nervousness/restlessness and excessive constant crying, the hypoglycaemic puppies develop a second stage with neuroglycopenic symptoms: letargy, absence suckling reflex, inactivity/atonny, mental weakness, depression, seizures/coma/death. After a first detection of the cut-off value of <40 mg/dl to identify hypoglycaemic puppies (Lawler, 2008), the blood



levels of glucose have been associated to puppies mortality, and different cut-off were proposed. In a study from Vassalo et al. (2015) the value of 40 mg/dl was associated to low Apgar score and poor reflexes, while mortality within 7 days of age was associated to 28 mg/dl (Vassalo et al., 2015). Mila et al. (2017) found that glucose values

<37 mg/dl at <8h were tended to be associated with mortality within 24 h (Mila et al., 2017), while values \leq 92 mg/dl at Day 1 were highly associated to death between Day 1 and Day 21 (Mila et al., 2017). Recently, Ballotta et al. (2019) reported that glucose value

<73 mg/dl identified at risk for mortality puppies on the basis of the Apgar evaluation.

On the opposite, Castagnetti et al. (2017) found a tendency to higher glucose in non-surviving puppies, and Antonczyk et al. (2021) reported that lower Apgar scores and higher risk of death were associated to higher glucose umbilical blood levels.

Finally, glucose level is considered not useful for predicting neonatal mortality, because it reflects maternal physiology and not fetal status by some authors (Vanspranghels et al., 2020; Lucio et al., 2021).

One study (Bolis et al., 2018) showed that the concentrations of glucose in amniotic fluid collected at birth in small-sized puppies was significantly lower (7 mg/dl; 0.5-11.7 mg/dl) in puppies non surviving at 24 h after birth in comparison to surviving ones (18 mg/dl; 12-30 mg/dl).

Hypothermia

Early after birth a transitory hypothermia is considered protective, but it becomes harmful when prolonged. Hypothermia is also a comorbidity in many neonatal pathologic conditions. In the short term, hypothermia can lead to low viability, low response to resuscitation. In the long term it relates to depression, absence/disappearance of suckling reflex, bradycardia, hypoglycemia, meteorism, ileo, necrotizing enterocolitis, aspiration pneumonia, immunity insufficiency, maternal neglect/cannibalism, neurologic disturbances/coma/death. The newborn puppy body temperature changes from birth along the neonatal period, so that different cut-off values have been detected for the time at birth and the neonatal period. In puppies >1h of age the cut-off for hypothermia was reported to be 35°C. A study from Vassalo et al. (2015) showed body temperature of 33.9 \pm 1.2 °C in puppies with mortality <7 days of age. Another study (Mila et al., 2017) found that body temperature <8 h tendency to be associated to death within 24 h of age

In general, small-sized newborns are considered at higher risk for hypothermia, probably due to the high surface/body mass ratio. During the neonatal period a body temperature of 35.5° C is considered as the cut-off value for hypothermia.

Malformations

Malformations or physical defects are very common in newborn puppies, with an incidence of (1-3%) 24.7% litter; 6.7% neonates. They can be structural or functional abnormalities; they can interfere with viability/weight gain; they can be of different severity degree. Single malformation (81.2%) or multiple malformations (18.8%) can be observed, and a breed predisposition to malformations is suspected, since the vast majority of them (84.4%) are observed in purebred dogs (Pereira et al., 2019)

A total 5.4% mortality rate was observed in newborns with congenital defect and corresponding to the 68.7% of the losses observed among those malformed, by Pereira et al. (2019). Most of death occur early after birth (0-2 d: 61.4%) and 38.6% occur between 3 and 30 days after birth. Death can occur because of euthanasia (16%), stillborn (16%), neonatal death (68%), unknown causes (54%), aspiration pneumonia (13.6%), cardiorespiratory insufficiency (6.8%), intestinal obstruction (6.8%), intestinal and urethral obstruction (2.3%). Among malformations, hydrocephaly (1.5%) is responsible for 11.3% mortality <4 weeks of age, while cleft palate (2.8%) for 50% mortality <4 weeks of age (Pereira et al., 2019).

Placental assessment

Placental impaired function is known to possibly affect neonatal outcome. However, unlike other domestic animal species, only recently the scientific interest for the study of the canine placenta arise. Interestingly, in a study from Tesi et al. (2020), a correlation between placental weight and birth weight in puppies was found. Very recently (Sarli et al., 2021) the histologic investigation and neonatal outcome



have been studied in dogs and multifocal confluent necrosis was associated to higher risk of death within 7 d (odds ratio 30.7).

Conclusions

In conclusion, an undoubted increasing interests for canine neonatology is observed. However, the still high perinatal mortality rates undelines the needed for suitable severity indicators for the newborn dog. In fact, although some first severity indicators have been detected, many (too) informations are still lacking.

The identification of newborn puppies at high risk of developing adverse outcomes at birth/hospitalization is the main goal in advancing veterinary neonatology, as well as the improvement of newborn assessment protocols.

Due to the strong differences between the characteristics of the newborn dog at the time of birth and during the neonatal period, time-specifying severity scoring systems should be developed for the puppy at birth and in the neonatal period. At birth assessment should include the maternal clinical examination, the newborn clinical examination (Apgar score, physical exam, BW, malformations, T°), neonatal blood gas analysis (pH, pCO₂, BE, bicarbonate, lactate), and also the placental assessment.

Only thanks to a systematic, well designed evaluation it will be possible to decrease perinatal mortality rate in dogs that still represents a challenge for the veterinarians.

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