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2 # Medetomidine premedication for caesarean section in the bitch,

3 # Is it safe for the dam and the puppies?

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9 This study shows that medetomidine hydrochloride in the protocol used is a safe premedicant in

10 bitches prior to caesarean section and is associated with good puppy vigour as well as 2 h and 7 d

11 puppy survival rates.

12 **1. Introduction**

13 The ideal anaesthetic protocol for caesarean section (CS) should provide adequate muscle

14 relaxation, analgesia and narcosis for optimal operating conditions, be safe for the bitch [2] and

15 should not affect the viability and survival of the puppies [3,4]. Additional recommendations include

16 using drugs with a short duration of action [5] and using drugs which are reversible [6]. Induction

17 using propofol and maintenance of anaesthesia using isoflurane is widely accepted and

18 associated with good outcome [4,7-12]. The use of alpha-2-adrenergic agonists before anaesthesia

19 for CS, is however, controversial. The alpha-2-adrenergic agonist xylazine, is not recommended in

20 patients undergoing CS because it was identified as a risk factor for increased puppy mortality

21 [12,13], associated with increased risk of death in the dog [14,15] and caused severe maternal and

22 neonatal cardiovascular depression [16].

23   The greatest objection to the use of the alpha-2-adrenergic agonists are the cardiopulmonary

24   effects which include transient hypertension followed by mild hypotension, bradycardia,

25   increased systemic vascular resistance, reduced cardiac output, and respiratory depression. In

26   recent surveys of anaesthetic mortality in the dog however, premedication with medetomidine

27   prior to anaesthesia for routine surgery, was not identified as an increased risk factor for

28   mortality [17] and data from human literature has shown that dexmedetomidine is associated with

29   a reduction in all causes of mortality when used for non-cardiac, cardiac and vascular surgery [18,19].

30   No studies in veterinary medicine have been conducted on the use of medetomidine for CS.

31   This study assessed puppy vigour and survival following medetomidine, propofol and sevoflurane

32   anaesthesia for elective CS.

33   **2.   Materials and Methods**

34   This is a retrospective, descriptive study that included 292 CSs in 256 privately owned bitches

35   which underwent a CS and were selected from the general obstetric population because of

36   increased obstetric risk. High-risk pregnancies in the current study were considered those

37   occurring in bitches from breeds with a high risk of complicated parturition [20], with a history of

38   dystocia [21], or with known very large litters [22]. All the bitches were admitted 3 to 4 d prior to the

39   predicted parturition date calculated as 57 d following D0. During these days, the bitches were

40   observed for signs of impending parturition (panting, inappetence, nesting behaviour, tenesmus)

41   and by 6 hourly vaginal speculum examinations to assess the cervix. The decision on when to

42   perform a CS was based upon the first appearance of any degree of dilatation of the cervix. Once

43   the decision to perform a CS was made, an ultrasound examination of the abdomen was

44   performed to establish if there were any dead foetuses (absence of detectable heartbeat).

45   Starting at induction, fluid therapy commenced and the PCV before and after CS determined as

46   previously described [23]. All bitches weighed more than of 20 kg. The anaesthetic protocol used in

47   the current study included the alpha-2-adrenergic agonist medetomidine hydrochloride

48 (Domitor®, Zoetis Animal Health, Sandton, South Africa) at 7 μg/kg iv as a premedicant, followed

49 one minute later by propofol (Fresenius propoven®1%, Fresenius Kabi, Midrand, South Africa) at 1

50 to 2 mg/kg iv as an induction agent. The propofol was administered as follows, the calculated

51 dose of 2 mg/kg was drawn up in syringe and 1 mg/kg/iv was administered as a bolus. The

52 remaining propofol was used as top-up if required. This was followed by immediate intubation

53 and inhalation of room air. Following surgical preparation (averaging 3 to 5 min), the bitch was

54 connected to a closed-circuit anaesthetic machine with 2% sevoflurane (Sevoflo®, Safeline

55 Pharmaceuticals, North Cliff, South Africa) in oxygen for maintenance of anaesthesia. The CS was

56 performed in standard fashion as described [24]. Meloxicam (Metacam®, Boehringer Ingelheim,

57 Randburg, South Africa) was administered iv (0.1 mg/kg) intra-operatively as previously proposed

58 [25], immediately after delivery of the last puppy. The processing of puppies following delivery

59 involved immediate administration of atipamezole hydrochloride (Antisedan®, Zoetis Animal

60 Health, Sandton, South Africa) at the dose of 50 μg/puppy sc, tying off of the umbilicus and

61 applying 10% povidone iodine thereto, drying the puppies, gently shaking fluids from their

62 airways and placing them in an air-heated incubator set at 35°C. No oxygen support was offered

63 to the puppies after delivery. Also, immediately after surgery, atipamezole hydrochloride at the

64 dose of 20 μg/kg was administered iv (extra label route of admin) to the bitch. The bitch was

65 observed until the coughing reflex returned and was then extubated and observed until she was

66 breathing comfortably whilst in sternal recumbency, sitting upright or standing. It was recorded if

67 the bitches were fully ambulatory within 15 minutes following extubation. After delivery of the

68 puppies the following records were made; total number of puppies delivered, live puppies, dead

69 puppies, deformed puppies and puppies euthanized. The Apgar scores were assessed starting

70 with the first puppy 15 min after the last puppy was delivered according to the methods

71 published [26] and later used by [27]. The bitch and puppies were discharged usually 2 to 3 h following

72 surgery.

73 The puppy survival rate was established immediately after delivery, at 2 hours post CS and 7 days

74 post CS and the maternal survival rate was established after delivery of the last puppy, at 2 h and

75 at 7 d post CS. The Glasgow pain scale evaluation was performed at the time of discharging the

76 bitch according to Glasgow Composite Measure Pain Scale to ensure adequacy of pain

77 management [28].

78 3. Results

79 A total of 292 CS were performed, 148 on 133 Boerboel bitches, 84 on 68 English bulldog bitches

80 and 60 on 55 other purebred bitches, which resulted in a total of 2232 puppies (1378, 541 and

81 313, respectively, per breed). Thirty-six bitches underwent more than one CS in this study. The

82 percentage of puppies live at delivery for the Boerboel, English bulldog and other purebred's

83 puppies respectively was; 97.39%, 96.67% and 91.69%. The 2 h survival rate was 95.43%, 88.35%

84 and 89.78% and the 7-day survival rate was 89.19%, 79.11% and 84.03% respectively. The

85 numbers of puppies euthanized due to malformation were 16/1378 (1.16%), 32/541 (5.59%) and

86 4/313 (1.28%) respectively for Boerboels, English bulldogs and other purebred dogs.

87 Thirty-five, 18 and 26 Boerboel-, English bulldog and other purebred puppies were stillborn. Of

88 these, 12 (34%), 9 (50%) and 15 (58%) had, respectively, been found dead on ultrasound

89 examination immediately before the CS was performed.

90 After correction for foetuses discovered dead on ultrasound and malformed euthanized puppies,

91 the survival rates for Boerboel-, English bulldog and other purebred puppies were 98.21%,

92 95.60% and 94.30%, respectively, at 2 hours and 91.78%, 87.17% and 88.26% at 7 days.

93 The Apgar scores averaged 9.66 for all the breeds combined, and 9.77, 9.35 and 9.68 for

94 Boerboel, English bulldogs and other purebred breeds respectively. The maternal survival rate

95 was 291/292. One Boerboel bitch died from gastric dilatation and volvulus 2 days following

96 surgery. The average Glasgow pain scale for bitches at discharge was 6.4 (S.D. 0.65, with a

97   minimum of 5 and a maximum of 8, n = 292). No bitch had a PCV of below 30% after surgery and

98   all bitches were fully ambulatory 15 minutes after extubation.

99   4. Discussion

100   The prime objectives for using premedication in any patient prior to surgery and CS is to reduce

101   the induction dose of anaesthesia [5], reduce the minimum alveolar concentration of inhalation

102   anaesthetics [6], decrease maternal stress and anxiety [29], provide analgesia and providing chemical

103   restraint allowing preoperative preparation in cases where this is required. The use of alpha-2-

104   adrenergic agonists meet all these requirements as they are potent sedatives, may induce

105   narcosis at high doses, act as analgesics [30], vastly reduce induction doses of propofol [31] and

106   reduces minimum alveolar concentration of isoflurane and sevoflurane [32-35].

107   Analgesics and non-steroidal anti-inflammatory agents in pregnant animals and humans are

108   problematic for CS [36-49]. Opioids provide analgesia but cross the placenta and can cause

109   significant central nervous system and respiratory depression in neonates [49] which may take 2 to

110   6 d in canine neonates to eliminate [25]. There is consensus that a single intravenous administration

111   of meloxicam at a dosage of 0.1 mg/kg immediately after delivery of the puppies is safe [25]. Failing

112   to administer analgesics for obstetric surgery has become unacceptable in the veterinary

113   profession and its legislative bodies. The analgesic properties of medetomidine intra-operatively

114   and post-operatively have been demonstrated [50] and reviewed in the dog [51] and demonstrated in

115   the pregnant woman before and after CS without adverse neonatal effects [52]. However, reversal

116   by atipamezole will also reverse the analgesic effects and therefore the administration of other

117   analgesics in the recovery and immediate post-operative period are indicated.

118   Although both maternal and neonatal cardiovascular depression associated with the use of

119   medetomidine may have been present in the current study, our results show that it did not

120   appear to affect puppy survival rate, Apgar score or maternal survival rate. The route of

121 administration of medetomidine is important as the iv route requires a much smaller dose to

122 achieve the same effect as opposed to the im route [53].

123 In the absence of premedication, the dose of propofol required to induce and intubate pregnant

124 bitches approaches 6 mg/kg [27]. A significant reduction of the induction dose of propofol, reducing

125 it to 1 mg/kg was recorded when medetomidine is used as premedicant at doses of 20 to

126 40 µg/kg [31]. Despite the use of a lower dose of medetomidine in the current study, it was possible

127 to intubate and surgically prepare all bitches never exceeding a total dose of 2 mg/kg of propofol.

128 The rate of stillbirth and neonatal death is known to be relatively high in dogs with mortality

129 ranging from 17% to 30% within the first 8 weeks of life [54] and with asphyxia being the leading

130 cause of death [55,56]. Stillbirths and deaths within the first week were responsible for the majority

131 of these losses. In a large study involving 10,810 litters, the perinatal mortality was present in

132 24.6% of litters. In the same study, 4.3% of puppies were stillborn and another 3.7% died within a

133 week [57.] Survival was 92% in the first week, and only another 1% dying from 8 days to 8 weeks of

134 age [57]. The puppy survival rate in other studies varied from 92.4% to 88.1% [58-61]. In a study by

135 Moon *et al.* (1988), survival rates immediately, 2 hours and 7 days after delivery were 92%, 87%,

136 and 80%, respectively, for puppies delivered by CS (n = 3,410) and 86%, 83%, and 75%,

137 respectively, for 498 puppies born naturally. Moon *et al.* (1998) reported that in 76% of litters

138 delivered by CS, all the puppies were born alive. The maternal mortality rate was 1% [62]. Our

139 results show that medetomidine appeared not to have affected puppy survival rate and maternal

140 survival rate.

141 In a study involving 37 CSs performed on English Bulldogs, 14.9% of the puppies were stillborn,

142 8.2% of the puppies alive, were deformed; mainly cleft palate (palatoschisis) and anasarca, and

143 10% of the puppies died before the age of weaning [20]. This is similar to the 6.9% birth defects and

144 15.91%, 24 h mortality that Batista *et al.* (2014) reported for elective CS in English bulldogs. The

145 results from the current study in English bulldogs were similar with respect to the number of

146 deformed puppies (5.59%) but better for percent live birth (96.67%). In 193 puppies from 42

147 litters, 65 born by spontaneous delivery, 66 by assisted delivery and 62 by caesarean section, the

148 percentage of stillbirths were 14%, 20% and 8% respectively [26].

149 Puppy survival rates at birth and at 2 h after birth supposedly reflect the effects of perioperative

150 conditions more specifically than at 7 d after delivery [12.] This is because deaths within the first

151 week are often associated with factors relating to maternal care, agalactia, undetected birth

152 defects and infectious causes [54].

153 It is important to establish prior to a treatment or procedure whether all the foetuses are alive

154 and well prior to the intervention [63] to avoid a false overestimation of the effect of the

155 intervention on puppy mortality. Pre-operative ultrasound enables one to account for at least

156 some foetuses that died before and therefore those stillbirths may be considered independent of

157 the intervention. The current study identified 45.6% (36/79) of stillborn puppies on ultrasound

158 examination immediately before the CS was performed.

159 Because the aim of the current study was to evaluate the effect of our anaesthetic protocol on

160 puppy survival rates, puppy vigour and maternal survival rates, attempts were made to exclude

161 confounders which may have affected outcome not related to anaesthetic protocol. These were

162 foetuses detected dead on ultrasound examination prior to administering any drugs included in

163 the anaesthetic protocol and puppies euthanised because they were deformed. This correction is

164 particularly useful when comparing puppy survival rates of the English bulldog breed to those of

165 others. English Bulldog puppies not only have poorer survival rates at 2 h and at weaning age but

166 also an increased risk of being stillborn or being born with defects requiring euthanasia [20,64].

167 The maternal survival rate in this study was good as all but one of the 292 bitches anaesthetized

168 were alive at 7 days post CS. A single Boerboel bitch died from gastric dilatation and volvulus two

169 days after discharge. Gastric dilatation and volvulus is a well-recognized cause of sudden death

170　large breeds [65]. Therefore, our results support the finding by another worker that premedication

171　with medetomidine was not identified as an increased risk factor for anaesthesia in the dog [17]. In

172　contrast, xylazine has safety concerns for both dam and neonate when used for CS in the bitch [12-

173　16]. The demonstrated safety recorded in the current study may in part be explained by; improved

174　alpha 1 : alpha 2 specificity exhibited by medetomidine compared to xylazine, greater awareness

175　of the physiologic effects of alpha2-adrenergic agonists [17] and the use of a relative low dose

176　(7 μg/kg) of medetomidine. Although dexmedetomidine and medetomidine induced similar

177　clinical effects [66], there are theoretical pharmacological advantages of the non-racemic alpha2-

178　adrenergic agonist, dexmedetomidine, over medetomidine [67]. The primary author observed no

179　differences in clinical effects when medetomidine is replaced by dexmedetomidine.

180　Apgar scores have been shown to be influenced by anaesthetic agents. Alfaxalone (1 to 2 mg/kg)

181　has been shown to be slightly superior to propofol (2 to 6 mg/kg) in this respect [27,68]. Overall, the

182　Apgar scores achieved in the current study were higher than those reported in other studies

183　irrespective of method of delivery or anaesthetic protocol used [26,27, 68, 69]. The time at which Apgar

184　scores are measured after birth is important. Although in early studies in man, a score at one

185　minute was used [70], it was later demonstrated that the score at five minutes is more predictive of

186　survival [71]. Similarly, in puppies, evaluations performed at five minutes after birth were less

187　predictive than those done at 15 minutes and 60 minutes after delivery [26,27,69]. This may be

188　because more time was allowed to elapse for removal of depressive effects of the anaesthetic

189　agents before an Apgar score was evaluated. In the current study the delay from delivery till

190　Apgar score evaluation may have allowed for complete reversal of medetomidine in the puppy

191　and for the concentration of propofol in the central nervous system to diminish by redistribution

192　which is reported to take 15 to 20 min [8,72]. Furthermore, the low induction dose of propofol used

193　and atipamezole administration, may also have favourably influenced Apgar scores.

194 In agreement with the studies by others [27,26], the current study shows that Apgar scores correlate

195 with mortality, with lower scores being associated with higher mortality rates. Although another

196 study has shown that English Bulldog puppies were at increased risk compared to other breeds

197 for suffering from poor vigour after CS [11], our study showed only slightly reduced Apgar scores

198 when compared to other purebreds and Boerboel puppies. The method of delivery may impact

199 puppy vigour. In contrast to findings by others, we recorded higher Apgar scores for puppies from

200 caesarean deliveries than those of the eutocic vaginally delivered puppies reported in the

201 literature [73,74]. These differences may reflect the different anaesthetic protocols used in the

202 studies and the timing of obstetric intervention. Our results show that medetomidine appeared

203 not to have affected the Apgar score.

204 The effect of early intervention by CS (at the first observation of a dilated cervix), prior to foetal

205 compromise may in part explain the good results obtained in our study. This agrees with the

206 literature reporting positive correlation between timeous intervention and puppy survival [12,21,75-81]

207 **5. Conclusions**

208 This study shows that anaesthetic protocol using medetomidine hydrochloride at 7 µg/kg iv as

209 premedicant combined with 1 to 2 mg/kg propofol as induction agent and 2% sevoflurane in

210 oxygen as maintenance, is safe for CS in the bitch. The Apgar scores 15 min after delivery, as well

211 as the puppy and maternal survival rates at delivery, 2 h, and 7 d compare favourably to those

212 reported in publications using other anaesthetic protocols. The use of medetomidine as

213 premedicant permits the use of less than ½ the induction dose of propofol usually required when

214 no premedicant is used.

215 **6. Practical hints**

216 The prime author has been using medetomidine in more than 2000 CSs and in bitches of all sizes.

217 The weight (real mass not lean body mass) of the bitch requires discussion.

218   In this study, all anaesthetic subjects were 20 kg or more. It is however the experience of the

219   prime author when using medetomidine at 7 μg/kg for CSs in toy breeds, the dose of propofol

220   required to allow intubation approaches 2-3 mg/kg as opposed to 1-2 mg/kg. Furthermore, the

221   time allowed following induction and intubation in the prep room whilst not on gas inhalation, is

222   reduced when using medetomidine at the low dose of 7 μg/kg. Therefore, the author uses

223   10 μg/kg medetomidine premedication for CS in dogs under 20 kg with no observable differences

224   in outcome. Not all practices perform CSs frequently and many may not have sufficient

225   experienced staff to ensure rapid surgical preparation and neither do all prep rooms have access

226   to gas-inhalation anaesthesia. Therefore, if delays between intubation and connection to gas-

227   inhalation maintenance of anaesthesia are expected, the author advises using medetomidine

228   premedication at 10 μg/kg irrespective of the weight of the bitch and has observed no differences

229   in outcome when doing so. Practitioners are reminded that propofol is available in 1% and 2%

230   concentrations and should make sure that they adjust their volumes accordingly.

231

232   The question whether a bitch should be surgically prepped prior to premedication, after

233   premedication or after premedication, induction and intubation is not straight forward. Some

234   bitches are combative and will resist the restraint required to perform surgical preparation. Some

235   heavily pregnant bitches of any breed that are placed in dorsal recumbency desaturate whilst all

236   English bulldogs suffering from brachycephalic obstructive airway syndrome (BOAS) severely

237   desaturate when doing so (unpublished date, de Cramer). Furthermore, in heavily pregnant

238   bitches suffering from BOAS, the relaxation of the airway induced by premedication causes severe

239   desaturation (visible cyanosis) even in the patient that is not handled and remains in the standing

240   or sitting position (unpublished date, de Cramer). Because it cannot always be predicted how a

241   bitch will respond to restraint and because a substantial proportion of all CSs are performed on

242   brachycephalic bitches, the prime author prefers to surgically prepare all bitches following

243   induction and intubation.

244   The volume of the medetomidine at the doses described in this manuscript is small and therefore

245   accurate measurement of the required volume can more reliably made when using a 1 ml syringe.

246   Also, when using very small volumes in toy breeds, a significant volume of medetomidine may be

247   lost in the hub of the intravenous catheter and in the tip of the syringe and therefore extending

248   the medetomidine volume with ringers or saline may ensure administration of the full required

249   volume. Practitioners may be tempted to use the medetomidine intramuscularly in aggressive

250   bitches to allow for the placement of an intravenous catheter. Very large doses of medetomidine

251   are required intramuscularly to achieve this goal and this practice cannot be advised as its safety

252   has not been established.

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