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This is a pre print version of the following article:

Original

Effects of intravenous romifidine, detomidine, detomidine combined with butorphanol, and xylazine on tear production in horses / Leonardi, F.; Costa, G. L.; Dubau, M.; Sabbioni, A.; Simonazzi, B.; Angelone, M.. - In: EQUINE VETERINARY EDUCATION. - ISSN 0957-7734. - 32:S11(2020), pp. 53-57. [10.1111/eve.13040]

Availability:

This version is available at: 11381/2854565 since: 2021-10-06T17:32:41Z

Publisher:

Equine Veterinary Journal Ltd

Published

DOI:10.1111/eve.13040

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note finali coverpage

(Article begins on next page)

**EFFECTS OF INTRAVENOUS ROMIFIDINE, DETOMIDINE, DETOMIDINE
COMBINED WITH BUTORPHANOL, AND XYLAZINE ON TEAR PRODUCTION
IN HORSES**

1 **Running title:** effects of sedation on equine STT I values

2

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11 SUMMARY

12 Sedation facilitates the ocular examination in horses. Alpha2-adrenoceptor agonists are
13 commonly used in equine practice. If the eye is painful, the combination of an α 2-
14 adrenoceptor agonist and butorphanol provides a greater analgesic effect. Unfortunately, little
15 is known about the effects of α 2-adrenoceptor agonists on equine Schirmer tear test I (STT I)
16 values. The aim of the study was to assess the effects of intravenous romifidine, detomidine,
17 detomidine combined with butorphanol, and xylazine on the STT I values in horses. Forty
18 client-owned Italian saddle horses were enrolled. Horses received 0.04 mg/kg of romifidine
19 or 15 μ g/kg of detomidine or 10 μ g/kg of detomidine combined with 10 μ g/kg of butorphanol
20 or 0.7 mg/kg of xylazine intravenously. The Schirmer tear test strip was inserted into the
21 lateral third side of the inferior conjunctival fornix for one minute in each eye. The STT I
22 measurements were performed before sedation and at 5, 15, 30, 60, 120 and 180 minutes after
23 the administration of sedation. The data were analyzed by ANOVA. Romifidine did not
24 affect the STT I values. Detomidine significantly reduced the STT I values at 15 minutes
25 (18.17 ± 0.97 mm/min). The combination of detomidine and butorphanol significantly
26 reduced the STT I values at 30 and 60 minutes (17.44 ± 0.99 , 15.81 ± 0.99 mm/min).
27 Xylazine significantly increased the STT I values at 5, 15 and 30 minutes (25.17 ± 0.99 ,
28 26.72 ± 0.99 , 28.07 ± 0.99 mm/min). The STT I values at 180 minutes were similar to those
29 before sedation. These results suggest that the administration of xylazine or detomidine alone
30 or combined with butorphanol is associated with significant changes in aqueous tear
31 production, whereas romifidine does not affect the STT I values. Romifidine is therefore
32 suitable for chemical restraint to measure tear production in horses.

33

34 **Key words:** horse, Schirmer tear test I, sedation, α 2-adrenoceptor agonist, butorphanol

35

36 **INTRODUCTION**

37 The tear film confers the cornea an optical surface for the refraction of light, allows the
38 mechanical removal of debris and bacteria, and lubricates the conjunctiva (Martin 2005). If a
39 deficiency of the lacrimal system is supposed, the measurement of tear production is
40 mandatory (Crispin 2000). The Schirmer tear test I (STT I) is the most commonly used test to
41 measure the basal and reflex tear production in horses (Williams *et al.* 1979). Low STT I
42 values than 10 mm/min are pathological, whereas high values are not pathological because
43 horse's tear production may be as high as 35 mm/min (Hendrix 2005).

44 A single intravenous standard dose of an α 2-adrenoceptor agonist is commonly satisfactory to
45 perform a complete ocular examination in horses (Hendrix 2005). If the eye is painful, the
46 combination of an α 2-adrenoceptor agonist and butorphanol may be required to provide a
47 greater analgesic effect (Hendrix 2005; Muir 2009; Bianchi *et al.* 2015).

48 Alpha2-adrenoceptor agonists induce a dose-dependent, rapid and quite predictable effect
49 (Muir 2009). Romifidine, detomidine and xylazine are the most commonly used α 2-
50 adrenoceptor agonists in equine practice (Nannarone *et al.* 2007). They vary in potency,
51 duration of action, and side effects depending on α 2-adrenoceptor selectivity. Romifidine is
52 more potent than xylazine but it is less potent than detomidine (Muir 2009). Nevertheless,
53 0.04 mg/kg of romifidine appeared equipotent to 10 μ g/kg of detomidine, whereas 0.08
54 mg/kg of romifidine appeared similar in potency to 1 mg/kg of xylazine (England *et al.*
55 1992).

56 The duration of action of detomidine is longer compared to that of xylazine but shorter
57 compared to that of romifidine (Muir 2009).

58 With regard to side effects, the depression of cardiorespiratory function induced by xylazine
59 and romifidine is less marked than that caused by detomidine. Furthermore, romifidine and
60 detomidine induce less pronounced ataxia compared to that induced by xylazine (Muir 2009).

61 Butorphanol is a κ -opioid receptor agonist and a μ -opioid receptor antagonist. It is not
62 commonly used alone for an ocular examination because it may cause increased spontaneous
63 movements. The combination of butorphanol and α 2-adrenoceptor agonist synergistically
64 acts to improve sedative effects (Muir 2009).

65 Conflicting data about the effects of α 2-adrenoceptor agonists on equine STT I values have
66 been previously reported. Intravenous administration of 20 μ g/kg of detomidine or 150 mg of
67 xylazine significantly reduced the STT I values (Brightman *et al.* 1983; Ghaffari *et al.* 2017).
68 On the contrary, Marts *et al.* (1977) reported that xylazine had no demonstrable effect on tear
69 production in horses. To the authors' knowledge, there are no available data on the effects of
70 romifidine and detomidine combined with butorphanol on equine tear production.

71 The aims of the study were to evaluate the effects of intravenous romifidine, detomidine,
72 detomidine combined with butorphanol, and xylazine on tear production as assessed with the
73 STT I in horses and to evaluate the influence of the sex and right eye or left eye on the STT I
74 values after sedation.

75

76 **MATERIALS AND METHODS**

77

78 **Animals**

79 This study was performed in accordance with the Legislative Decree n. 26 of 4th March 2014
80 under Italian Animal Welfare Legislation and was approved by the Institutional Ethics
81 Committee for animal welfare of the University of Parma. The owners signed a voluntary
82 informed consent form prior to the horses' enrollment.

83 The inclusion criteria were as follow: adult Italian saddle horses undergoing a radiologic or
84 ultrasonographic assessment, no history of previous ocular disease, no drug therapy in the
85 previous two months, and normal complete blood count and biochemical profile.

86 The exclusion criteria were as follow: horses with abnormalities of the ocular surface or with
87 STT I values lower than 15 mm/min.

88

89 **Schirmer tear test I measurements**

90 An ocular examination consisting of a Schirmer tear test¹ and a slit lamp examination (SL-
91 17²) was performed before sedation. The strip was inserted into the lateral third of the inferior
92 conjunctival fornix for one minute in each eye. The STT I was performed first in the right
93 eye.

94 The STT I readings were performed before sedation, at 5, 15, 30, 60, 120 and 180 minutes
95 after the administration of sedation. The STT I measurements were performed in an enclosed
96 space under the same conditions of light, temperature and relative humidity. The same
97 experienced veterinarian blinded from the treatment performed the STT I measurements.

98

99 **Sedation protocols**

100 Food but not water was withheld for 12 hours prior to the administration of the sedation.
101 Horses were randomly (simple randomization with the computer-generated random numbers)
102 divided into four groups and were sedated with the corresponding drug intravenously. Horses
103 belonged to the group R received 0.04 mg/kg of romifidine (Sedivet³). Patients of the group
104 D were sedated with 15 µg/kg of detomidine (Domosedan⁴). Animals of the group DB
105 received 10 µg/kg of detomidine combined with 10 µg/kg of butorphanol (Nargesic⁵). Horses
106 of the group X were sedated with 0.7 mg/kg of xylazine (Megaxilor⁶).

107

108 **Data analysis**

109 The data were analyzed with ANOVA by means of the general linear model (GLM)
110 procedure in SAS Version 9.4⁷. The fixed factors included sedation protocol (four levels:

111 romifidine, detomidine, detomidine combined with butorphanol, and xylazine), time (seven
112 levels: before sedation, 5, 15, 30, 60, 120 and 180 minutes after the administration of
113 sedation), sex (three levels: intact females, intact males, spayed males) and eye (two levels:
114 right eye, left eye). The age (years) and weight (kg) of the horses were considered covariates.
115 The STT I values were reported as least-squares means (LSMeans) \pm standard error of the
116 mean (SEM). The age and weight were expressed as mean \pm standard deviation (SD). *P*
117 values < 0.05 were considered significant.

118

119 **RESULTS**

120 Forty adult Italian saddle horses were included in the study. Each group consisted of 10
121 subjects (Table 1). The STT I values are reported in table 2.

122 In the group R, there were no significant differences in the STT I values.

123 In the group D, the STT I value was significantly lower 15 minutes after the administration of
124 sedation compared to the values before sedation ($P = 0.007$), at 5 minutes ($P = 0.001$) and
125 180 minutes ($P = 0.001$).

126 In the group DB, the STT I value at 30 minutes was significantly lower compared to the
127 values before sedation ($P = 0.004$), at 120 minutes ($P = 0.046$) and 180 minutes ($P = 0.046$).

128 The STT I value at 60 minutes was significantly lower compared to the values before
129 sedation ($P = 0.001$), at 5 minutes ($P = 0.006$), 15 minutes ($P = 0.024$), 120 minutes ($P =$
130 $.001$) and 180 minutes ($P = 0.001$).

131 In the group X, the STT I values at 5, 15 and 30 minutes were significantly higher compared
132 to the value before sedation ($P = 0.001$). The STT I values at 5 and 15 minutes were
133 significantly higher compared to those at 60 minutes ($P_5 = 0.029$, $P_{15} = 0.001$), 120 minutes
134 ($P_5 = 0.013$, $P_{15} = 0.001$) and 180 minutes ($P_5 = 0.021$, $P_{15} = 0.001$). The STT I value at 30

135 minutes was significantly higher compared to those at 5 minutes ($P = 0.038$) and 120 minutes
136 ($P = 0.001$).

137 With regard to sex and right eye and left eye, no significant differences were recorded.

138

139 **DISCUSSION**

140 This study demonstrates that the administration of detomidine alone or combined with
141 butorphanol decreases tear production. Intravenous romifidine does not affect tear
142 production, whereas the administration of xylazine is associated with increased aqueous tear
143 production.

144 The choice of the most suitable α_2 -adrenoceptor agonist for sedation is critical for the success
145 of the ocular examination (Hendrix 2005). Detomidine is often used because it ensures a
146 steady head position even though it is associated with decreased tear production (Ghaffari *et al.*
147 *2017*). As expected, decreased tear production was recorded 15 minutes after sedation
148 because the peak of the sedative effects of detomidine is reached within 15 minutes after
149 intravenous administration (Muir 2009). Nevertheless, differently from previous findings
150 (Ghaffari *et al.* 2017), the significant decrease in tear production is no longer present 30
151 minutes after sedation. Based on the dose-related effects of detomidine (Muir 2009), the
152 probable reason is that the dose employed in the present study is lower compared to that used
153 by Ghaffari *et al.* (2017).

154 One explanation for the decreased measurable tear production after the administration of
155 detomidine is the evaporative losses increased by inadequate blinking caused by sedation
156 (Crispin 2000).

157 Nevertheless, the most likely causes for the reduction in aqueous tear production are the
158 neurophysiological mechanism and hemodynamic changes. Even though specific details of
159 the innervation of equine lacrimal glands are poorly known (Crispin 2000), it is likely that the

160 postsynaptic activation of α_2 -adrenoceptors in the central nervous system may have
161 decreased basal tear production. Furthermore, the reduction in the STT I values may be due
162 to the decrease in reflex tear production mediated by diminished nociceptive transmission,
163 which is modulated by α_2 - adrenoceptors (Martin 2005).

164 With regard to hemodynamic changes, detomidine induces mild hypotension that is
165 responsible for decreased perfusion of the lacrimal glands followed by a consequent decrease
166 in the STT I values (Muir 2009). Detomidine could have additionally caused a direct
167 vasoconstriction of the vessels of lacrimal glands.

168 Intravenous administration of the combination of detomidine and butorphanol is associated
169 with a more accentuated and prolonged decrease in tear production compared to that induced
170 by detomidine alone. Furthermore, horses belonged to the group DB showed the lowest STT I
171 values recorded in the present study even though the STT I values do not go below the
172 reference range reported in normal horses (Marts *et al.* 1997; Beech *et al.* 2003; Piccione *et*
173 *al.* 2008). These observations agree with those of similar studies in dogs (Dodam *et al.* 1998;
174 Sanchez *et al.* 2006) and underscore that opioidergic signalling pathways plays an important
175 role in tear production (Zagon *et al.* 2012). Moreover, it is likely that detomidine combined
176 with butorphanol may have additive and /or synergistic effects in decreasing equine tear
177 production improving analgesia and affecting hemodynamic changes and neurophysiological
178 mechanism (Muir 2009; Bianchi *et al.* 2015).

179 Another possible reason for the decreased measurable tear production caused by the
180 combination of detomidine and butorphanol is a potential opioid-induced alteration of the
181 metabolism of lacrimal glands (Mouney *et al.* 2011). Nevertheless, further studies are needed
182 to clarify the effect of intravenous butorphanol alone on tear production.

183 An ocular examination is usually a short procedure and romifidine is not therefore the most
184 suitable α_2 -adrenoceptor agonist because its duration of action is longer compared to those of

185 detomidine and xylazine (Muir 2009). Furthermore, based on a previous study demonstrating
186 that 0.04 mg/kg of romifidine reduced intraocular pressure in horses (Marzok *et al.* 2014), we
187 expected that the administration of romifidine was associated with decreased tear production.
188 Contradicting this expectation, romifidine did not affect the STT I measurements. The
189 probable reason for these results is that the dose of romifidine employed in the present study
190 is too low to affect aqueous tear production. Even though α 2-adrenoceptor agonists
191 commonly induce hemodynamic changes in a dose-dependent manner (Nannarone *et al.*
192 2007), we supposed that 0.04 mg/kg of romifidine did not markedly reduce cardiac output in
193 horses enrolled in this study, as it could have certainly happened with higher doses (Peboni
194 Figueiredo *et al.* 2005). Consequently, it is likely that a regular blood flow to lacrimal glands
195 was provided with no changes in the STT I values.

196 The effect of intravenous xylazine on tear production in horses has not been clearly
197 identified. It seems that xylazine alone has no direct effects on tear production (Marts *et al.*
198 1977), whereas intravenous administration of 150 mg of xylazine is associated with
199 decreased tear production in anesthetized horses ranged in age from 6 months to 14 years
200 (Brightman *et al.* 1983). Unfortunately, Brightman *et al.* (1983) did not report the dose of
201 xylazine expressed as mg/kg. However, our results contradict previous findings because
202 intravenous xylazine unexpectedly increased the STT I values. There are no reports in the
203 veterinary literature that can explain our results. It is likely that the increased measurable tear
204 production was due to ataxia, excitation, movement and the head “jerks” caused by xylazine
205 (Gilger *et al.* 2011). We suggest that this behavior may have increased complete blink rate
206 and, consequently, tear production (Crispin 2000). However, further studies are needed to
207 confirm this hypothesis.

208 With regard to the influence of sex and right or left eye on tear production, our results agree
209 with previous findings (Crispin 2000; Beech *et al.* 2003). In fact, in the present study, sex did

210 not influence the STT I values (Beech *et al.* 2003) and the second eye was not affected by the
211 stimulation of basal secretion in the first eye (Crispin 2000).

212 The present study shows some limitations related to environmental conditions, equipotency
213 of α 2-adrenoceptor agonists and head position.

214 The influence of time of day, season, and environment on tear production has not been
215 entirely clarified by researchers (Beech *et al.* 2003; Piccione *et al.* 2008). These factors do
216 not seem to influence the STT I values even though a circadian rhythm of tear production was
217 reported (Beech *et al.* 2003; Piccione *et al.* 2008). In the present study, the influence of these
218 variables on the STT I values was not investigated.

219 Another limitation of the study is that we did not accurately evaluate the equipotency of α 2-
220 adrenoceptor agonists. We chose approximate equipotent doses based on the veterinary
221 literature (England *et al.* 1992; Nannarone *et al.* 2007).

222 Head position and height of the eye above the level of the heart affect intraocular pressure but
223 no report investigated the influence of these variables on tear production (Holve 2012).

224 Consequently, we cannot clearly exclude an influence of these factors on the STT I
225 measurements.

226 In conclusion, intravenous administration of romifidine does not affect aqueous tear
227 production and may be useful to measure tear production in horses undergoing ophthalmic
228 procedures requiring sedation. Xylazine increases tear production and is not suitable for
229 chemical restraint to perform a complete ocular examination in horses. The administration of
230 detomidine alone or combined with butorphanol reduce the STT I values and the use of
231 ophthalmic ointments is therefore recommended after sedation.

232

233 **AUTHORS' DECLARATION OF INTERESTS**

234 No conflicts of interest have been declared.

235

236 **ETHICAL ANIMAL RESEARCH**

237 This study was performed in accordance with the Legislative Decree n. 26 of 4th March 2014
238 under Italian Animal Welfare Legislation and was approved by the Institutional Ethics
239 Committee for animal welfare of the University of Parma.

240

241 **ACKNOWLEDGEMENTS**

242 The authors would like to remember Stefano Zanichelli, full professor of veterinary surgery
243 who passed away on 9th December 2015. We really wish to thank him for, over the past
244 years, working tirelessly to support scientific research.

245

246 **AUTHORSHIP**

247 F. Leonardi, B. Simonazzi, M. Dubau and M. Angelone designed the study. G.L. Costa and
248 A. Sabbioni undertook the statistical analyses. All authors contributed and commented to the
249 manuscript and read and approved the final version.

250

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259

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- 318

319 **TABLES**

320

321 **Table 1.** Sex, age and body weight of horses belonged to the four groups

	Group R (n = 10)	Group D (n = 10)	Group DB (n = 10)	Group X (n = 10)
Sex				
<i>Number of intact females</i>	6	3	2	6
<i>Number of intact males</i>	2	3	3	2
<i>Number of spayed males</i>	2	4	5	2
Age (year)				
<i>Mean ± standard deviation</i>	23.3 ± 6.46	12.3 ± 7.64	15.8 ± 7.99	22.5 ± 6.45
<i>Range</i>	15-33	3-22	3-33	15-33
Body weight (kg)				
<i>Mean ± standard deviation</i>	492.5 ± 46.70	429.8 ± 54.32	500.8 ± 64.62	488 ± 36.80
<i>Range</i>	426-574	351-506	394-608	430-570

322 R = romifidine; D = detomidine; DB = detomidine combined with butorphanol; X = xylazine;

323 n = number of horses

324

325 **Table 2.** STT I values (mm/min) before sedation and at 5, 15, 30, 60, 120 and 180 minutes
 326 after the administration of sedation in the four groups. STT I values are expressed as least-
 327 squares means \pm standard error of the mean (SEM)

	Before sedation	5 min	15 min	30 min	60 min	120 min	180 min	SEM
Group R	24.18	24.23	25.18	24.83	23.33	22.88	23.93	1.00
Group D	21.48 ^b	20.79 ^a	18.17 ^{a,b,c}	20.17	19.33	20.44	22.51 ^c	0.975
Group DB	21.06 ^{a,c}	19.27 ^b	18.69 ^d	17.44 ^{c,f,n}	15.81 ^{a,b,d,e,r}	19.99 ^{n,r}	20.44 ^{e,f}	0.988
Group X	20.88 ^{a,b,c}	25.17 ^{a,d,f,h,i}	26.72 ^{b,e,l,m}	28.07 ^{c,f,g}	22.13 ^{d,e}	21.73 ^{g,h,l}	21.93 ^{i,m}	0.999

328 R = romifidine; D = detomidine; DB = detomidine combined with butorphanol; X = xylazine;

329 min = minutes

330 In the same row, the same superscript (^{a,b,c,d,e,f,g,h,i,l,m,n,r}) marks the values with a statistically

331 significant difference between them ($P < 0.05$).