

Sedative and clinical effects of the pharmacopuncture with xylazine in dogs¹

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ABSTRACT

PURPOSE: To investigate the sedative and clinical effects of the pharmacopuncture with xylazine, compared to the conventional dose of a intramuscular injection in dogs.

METHODS: Twelve dogs were randomly distributed in two groups of six animals and treated as follows: control group (X-IM): 1mg kg⁻¹ of xylazine given intramuscularly (IM); pharmacopuncture group (X-Yintang): 0.1mg kg⁻¹ of xylazine diluted to 0.5 mL of saline injected into the Yin Tang acupoint. Heart rate, cardiac rhythm (ECG), systolic arterial blood pressure (SABP), respiratory rate (RR), rectal temperature (RT), blood glucose concentration, degree of sedation and adverse effects were evaluated.

RESULTS: Sedative effect was observed in both groups. The degree of sedation was greater in X-IM only at 15 min when compared with X-Yintang group. Cardiovascular established was observed in X-Yintang group, while marked reduction in the HR and increased incidence of ECG abnormalities were detected in X-IM. In both treatment groups, minimal changes were observed in relation to SABP, RR, RT and blood glucose. High incidence (66%) of vomiting was observed in X-IM, while this adverse effect was absent in X-Yintang.

CONCLUSION: Pharmacopuncture with xylazine induced clinically relevant sedative effects in dogs, with the advantage of reduction of undesirable side effects associated with α_2 -agonists, including bradycardia, cardiac arrhythmias, and emesis.

Key words: Acupuncture. Sedation. Anxiolytic Agents. Xylazine. Dogs.

Introduction

Alpha₂adrenoreceptor agonists (α_2 -agonists) have several characteristics that make them attractive as premedication for general anesthesia. These include sedation, anxiolysis, analgesia, prevention of autonomic reflex response, reduced anesthetic requirements, improved intraoperative stability and facilitation of induction of anesthesia¹⁻³.

Xylazine^{4,5}, romifidine^{6,7}, medetomidine^{8,9} and dexmedetomidine^{10,11} have all been used in dogs for sedation and anesthetic premedication. However, α_2 -agonists, through stimulation of central and peripheral adrenoreceptors, significantly affect cardiovascular function, which becomes most significant in sick, unstable, or cardiovascular compromised patients¹⁻³. The main negative cardiovascular effects of all α_2 -agonists include bradycardia and associated arrhythmias (1st and 2nd degree atrioventricular heart block), a dramatic reduction in cardiac output by up to 50%, and an increase in systemic vascular resistance (SVR)^{3,4}.

The hemodynamic effects are typically dose related with the administration of α_2 -agonists. Lower doses of these drugs may be associated with more predominant central nervous system (CNS) effects, whereas higher doses probably cause a more pronounced stimulation of peripheral adrenoreceptors and vasoconstriction^{1,4}.

Pharmacopuncture, the injection of subclinical doses of drugs into acupoints, has been proved to be a very successful practice in domestic animals¹²⁻¹⁴. A micro-dose of acepromazine (1/10 of the conventional dose) injected into the Yin Tang acupoint in dogs reduced in 32% the dose of thiopentone for induction of anaesthesia compared to 51% in animals treated with the full dose administered subcutaneously. These data suggest an improvement of the sedative effect produced by acepromazine when administrated into the Yintang acupoint¹².

According to Traditional Chinese Medicine, the acupoint Yin Tang has a sedative effect in humans and animals¹⁵⁻¹⁸. In people, acupressure and manual acupuncture on the Yin Tang point was associated with pronounced changes in the bispectral index (BIS) values, with significant sedative effect^{17,18}.

The aim of this study was to investigate the sedative and clinical effects of the pharmacopuncture with xylazine (1/10 of the dose), compared to the conventional dose of an intramuscular injection in dogs.

Methods

This study was approved by the Institutional Animal Research Ethical Committee (protocol number 563/10).

Twelve mixed breed dogs, weighting 10±2kg were evaluated in this study. Health status was established on the basis of a physical examination and normal complete blood count, biochemistry perfil and electrocardiogram using standard methods.

After withdrawal of food and water for 12 and 3 hours, respectively, the dogs were randomly assigned to receive one of the following two treatments, in a double-blind design: the control group (X-IM) received 1mg kg⁻¹ intramuscular (IM) xylazine (Rompum, Bayer do Brazil, São Paulo, Brazil) and pharmacopuncture group (X-Yintang) received 0.1mg kg⁻¹ of xylazine diluted to 0.5 mL of saline solution injected into the Yin Tang acupoint, located on the dorsal midline of the head between the eyebrows (Figure 1).



FIGURE 1 - Location of Yin Tang acupoint in dogs. Available from: <http://www.animalacupressure.com/page.aspx?id=193>

The following measurements were performed: Heart rate (HR) and rhythm (ECG) were monitored using a cardiac monitor (TEB, ECG, São Paulo, Brazil); systolic arterial blood pressure (SABP) was measured by noninvasive method using a Doppler ultrasonic (Doppler 841-A, Parks Medical Electronics, Las Vegas, EUA), adapting the cuff around the radius; respiratory rate (RR) was measured by the observation of thoracic movements for one minute; rectal temperature (RT), using a digital thermometer (BD, Minas Gerais, Brazil). HR, ECG, SABP and RT measurements were made before and every 15 min for 60 min after injection of the treatments.

Venous blood samples were collected from the cephalic vein to measure of glucose prior xylazine administration and after 30, and 60 min. Blood samples for glucose measurements were immediately analyzed by amperometry in a portable glucometer (Accu-Check Aviva - Roche Diagnostics Corp. – Indianapolis-IN, USA).

The degree of sedation was scored on a 5-point scale as follows: alert (0) = no motor deficits, equivalent to pre-baseline; faint sedation (1) = stands, walks, some ataxia and disorientation; light sedation (2) = stands but ataxic, can remain sternal; mild sedation (3) = cannot stand, can remain sternal, may struggle; moderate sedation (4) = can raise head, usually laterally

recumbent; heavy sedation (5) = nonresponsive, cannot raise head⁸. Measurements were performed before and at 15, 30, 45, and 60 min after drug injection.

Data are collected by a single investigator who was blinded to the treatments throughout the experiment, following the same order (degree of sedation, cardiopulmonary parameters, rectal temperature and blood samples collection).

The data were analyzed using Graphpad software. Main effects of treatment or time within each treatment group were evaluated using analysis of variance for repeated measures. In analyses that demonstrated a significant main effect, pairwise comparisons of the appropriate means were made using Tukey's method for multiple pairwise comparisons. For sedation score, the

Mann-Whitney test was applied. In all tests, statistical significance was assigned to $p < 0.05$.

Results

At baseline, there were no significant differences between the two groups in HH, ECG, SABP, RR, RT, blood glucose and sedation score.

Xylazine IM significantly decreased the heart rate. The lowest heart rate was 40 beats per minute and it occurred from 30 to 45 min post-xylazine injection (X-IM). Five of six X-IM dogs showed bradyarrhythmia, whereas in X-Yintang treatment group, bradyarrhythmia was not observed (Table 1).

TABLE 1 - Heart rate (HR), respiratory rate (RR), systolic arterial blood pressure (SABP), rectal temperature (RT) and blood glucose in dogs treated with xylazine (1 mg kg^{-1}) injected intramuscularly (X-IM, n=6) and xylazine (0.1 mg kg^{-1}) injected into Yintang acupoint (X-Yintang, n=6).

Variable	Time after xylazine injection (min)				
	Baseline	15	30	45	60
HR (beats min^{-1})					
X-IM	112±26	52±7*#	51±11*#	54± 11*#	60±15*#
X-Yintang	99±17	86±15	81±10	86±10	91±10
RR (breaths min^{-1})					
X-IM	38±16	18±7	15±8*	13±5*	12±2*
X-Yintang	27±8	24±6	20±3	18±3*	19±3*
SABP (mmHg)					
X-IM	115±8	106±14	91±3*#	94±5#	100±12
X-Yintang	123±10	120±12	113±5	118±10	117±10
RT (°C)					
X-IM	38±0.2	38±0.2	38±0.5	37±0.5*#	37±0.7*#
X-Yintang	38.5±0.4	38±0.3	38±0.2	38±0.2	38±0.2
Glucose (mg mL^{-1})					
X-IM	80±6	-----	84±9	-----	92±12#
X-Yintang	78±9	-----	81±10	-----	75±9

Values are shown as mean±SD. *Significantly different from baseline values ($P < 0.05$). #Significantly different from X-Yintang treatment ($p < 0.05$).

In addition, a higher incidence of ECG abnormalities (sinus arrest, first degree AV block, second degree AV block) were observed in X-IM group (Table 2).

The systolic arterial blood pressure did not change between treatment groups, except from 30 to 45 min, when this parameter was lower in X-IM group in comparison with X-Yintang group (Table 1). In X-IM group, SABP was significantly lower at 30 min after xylazine administration when compared with the baseline values (Table 1).

TABLE 2 - Cardiac arrhythmias observed in dogs treated with xylazine (1 mg kg^{-1}) injected intramuscularly (X-IM, n=6) and xylazine (0.1 mg kg^{-1}) injected into Yintang acupoint (X-Yintang, n=6).

Groups	Cardiac arrhythmias#		
	SA	1st degree AV heart block	2nd degree AV heart block
X-IM	5/6	3/6	1/6
X-Yintang	----	----	----

#N° of dogs showing arrhythmia/N° of dogs evaluated.

Respiratory rates were not significantly different between the treatment groups at any time point. However, lower RR was observed from 30 to 60 min after the drug injection, when compared with the baseline values in both groups (Table 1).

Rectal temperature was lower from 45 to 60 min in X-IM treatment group when compared with X-Yintang treatment group.

Minimal changes were observed in blood glucose concentration. Dogs from the X-IM group had blood glucose significantly higher than dogs from the X-Yintang group only at 60 min after xylazine injection (Table 1).

Vomiting was observed in four of the six dogs in X-IM (66.6%), while no vomiting occurred in X-Yintang group.

The change in sedation scores following treatment administration was significantly different from baseline in both treatment groups. The greatest score sedation was observed at 15 and 30 min, respectively in X-IM and X-Yintang groups. The level of sedation tended to be higher in X-IM group than in X-Yintang group, but this difference was significantly only at 15 min after xylazine injection (Figure 2).

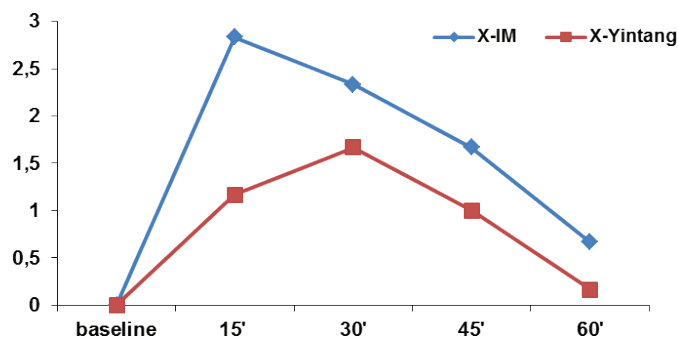


FIGURE 2 - Median sedation scores in dogs treated with xylazine (1mg kg⁻¹) injected intramuscularly (X-IM, n=6) and xylazine (0.1 mg kg⁻¹) injected into Yin Tang acupoint (X-Yintang, n=6). *Significantly different from baseline values (p<0.05). #Significantly different from X-Yintang treatment (p<0.05). Times listed are 15, 30, 45 and 60 minutes following xylazine injection

Discussion

Despite the desirable clinical properties of the α_2 -agonists, the main limiting factor of their use is the adverse cardiovascular effect¹⁻³. Marked decreases in heart rate and cardiac output, increases in total vascular resistance, and transient changes in blood pressure, are expected dose-dependent effects of xylazine^{1,2}.

It is well-established that administering xylazine consistently produces bradycardia^{1,4,5}, and the results of the current study support this finding. As expected, the majority of the dogs in the X-IM group showed bradycardia (HR<60bpm), while

this effect was not evidenced in the X-Yintang group. This finding confirms the dose-dependent cardiovascular depression induced by xylazine². In addition, sinus arrest, first and second degree AV block occurred only in X-IM treated dogs. Sinus and AV block induced by α_2 -agonists are often associated with bradycardia and attributed to decreased sympathetic outflow from the central nervous system and increased vagal tone³.

Several studies have shown that arterial blood pressure has a biphasic response when α_2 -agonists drugs are administered^{7,8}. In this study, we did not observe an initial increase in SABP in either of the groups. This result supports the findings of Monteiro *et al.*⁵ following xylazine IM injection at a dose of 0.5 and 1mg kg⁻¹ in dogs. The characteristics of the blood pressure changes appear to be in part determined by dose. Higher doses cause longer duration hypertension associated with a persistent increase in SVR^{2,3}. At lower doses, central effects predominate and blood pressure decreases to pre-treatment or below pre-treatment values^{6,19}. Furthermore, another studies have shown that arterial blood pressure has a biphasic response observed after intravenous administration, but not after intramuscular administration^{4,19}. In our study, arterial pressure decreased after xylazine treatment in both groups, which may be attributed to the sedative effect induced by α_2 -agonists drugs. Additionally, in X-IM group this effect may have been increased by the bradycardia⁸.

Xylazine has little effect on pulmonary function when administered at clinical doses. However, transient dose-dependent decreases in respiratory rate have also been reported^{1,2,19}. In our study, although median RR decreased significantly in both treatment groups, the decrease was unlikely to be clinically relevant, which is in agreement with other studies in dogs^{5,20}.

Previous studies have reported a decrease in body temperature in dogs given α_2 -agonists^{5,7}. This effect is thought to result from decreased heat production secondary to muscle relaxation or from a direct effect of the drug within the thermoregulatory system¹⁹. In the present study, despite mild reduction in the rectal temperatures, body temperatures remained within clinically acceptable limits in both groups.

Transient hyperglycemia have been reported in several species sedated with xylazine or that are anesthetized using a regime that incorporates xylazine^{21,22}. Blood glucose values tended to be higher in X-IM than X-Yintang, although significant difference was observed only at 60 min after xylazine injection. This result is in agreement with early studies that showed increased glucose values dose-dependently following xylazine treatment^{23,24}.

Vomiting has previously been reported following the administration of xylazine to dogs^{2,5}. Alpha₂-agonists typically

induce vomiting by stimulating the chemoreceptor trigger zone, which is in close proximity to the locus coeruleus in the brain^{1,2}. Xylazine induces vomiting during early sedation in as many as 50% of dogs and 90% of cats³. In the present study, the prevalence of vomiting in dogs which received xylazine IM was nearly 66%, whereas in Yin Tang xylazine treated dogs, the prevalence of vomiting was reduced to 0% and this might be attributable to the low dose used in this treatment group. These finds support the effect of pharmacopuncture to enhance the effect of subclinical doses of drugs, with the advantage of reduction of undesirable side effects, as described by Luna *et al.*¹³.

Based on the sedation score, mild to moderate sedation was produced in the X-IM group, with the maximal sedative effect observed at 15 min following xylazine injection. As expected, sedation started quickly due the fast activation of the presynaptic α_2 receptors^{1,2}. Xylazine is rapidly absorbed after IM injection, resulting in maximum plasma concentration after 15 min²⁵. On the other hand, 1/10 of the dose of xylazine in the Yin Tang acupoint induced slight to mild sedation, with the maximal sedative effect observed at 30 min after injection. The slow onset in X-Yintang group was expected, because the administration in an acupoint results in a subcutaneous absorption¹².

The sedative effect established in X-Yintang treatment group is consistent with previous reports, showing the potentiation effect of subclinical doses of drugs injected in an acupoint, i.e. pharmacopuncture¹²⁻¹⁴. In horses, 1/10 of the dose of acepromazine at GV1 acupoint was able to maintain a certain degree of sedation at 60 min, indicating a long-lasting effect of pharmacopuncture¹³.

Several acupoints may be used for analgesia in surgical procedures and also for sedation²⁶⁻²⁹. Kim and Nam²⁸ showed sedative effect following an acupuncture application in the Yintang and GV20 acupoints in conscious dogs.

The mechanism by which acupuncture produces analgesia and sedation remains unclear. However, the opioid system and the adrenergic system have been considered to play important roles in mediating the effects of acupuncture³⁰⁻³².

Recent studies have investigated the role of central norepinephrine (NE) in acupuncture^{33,34}. It was reported that acupuncture reduced NE levels in certain brain areas as well as in the blood circulation³⁵. Similarly, the sedative effect mediated by α_2 -agonists is linked with receptors located primarily in locus coeruleus neurons on the pons and lower brainstem³⁶. Alpha2-agonists bind with and intrinsically change the membranes of the α_2 -adrenoreceptors, preventing further release of the neurotransmitter NE. Centrally, NE is necessary for arousal. If the release of norepinephrine is blocked, the net result is sedation^{2,3}.

In addition, previous studies have reported that the sedative effect of acupuncture may be reversed by the administration of a α_2 -adrenergic receptor antagonist, such as yohimbine^{36,37} or atipamezole³². Based on these finds, the sedative effect observed in the X-Yintang group, may, at least in part, be attributed to the activation of the α_2 -adrenergic system induced by the acupoint stimulation mediated by the subclinical dose of xylazine administration.

Conclusion

Pharmacopuncture with xylazine induced clinically relevant sedative effects in dogs, with the advantage of reduction of undesirable side effects associated with α_2 -agonists, including bradycardia, arrhythmias, and emesis.

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