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Original article

Peripherally acting α-adrenoceptor antagonist MK-467 with intramuscular medetomidine and butorphanol in dogs: A prospective, randomised, clinical trial

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ABSTRACT

The aim of this study was to investigate the clinical usefulness of MK-467 (vatinoxan; L-659'066) in dogs sedated for diagnostic imaging with medetomidine-butorphanol. It was hypothesised that MK-467 would alleviate bradycardia, hasten drug absorption and thus intensify the early-stage sedation. In a prospective, randomised, blinded clinical trial, 56 client-owned dogs received one of two IM treatments: (1) 0.5 mg/m^2 medetomidine + 0.1 mg/kg butorphanol (MB, $n = 29$); or (2) 0.5 mg/m^2 medetomidine + 0.1 mg/kg butorphanol + 10 mg/m^2 MK-467 (MB-MK, $n = 27$). Heart rates and visual sedation scores were recorded at intervals. Plasma drug concentrations were determined in venous samples obtained approximately 14 min after injection. Additional sedation (50% of original dose of medetomidine IM) and/or IM atipamezole for reversal were given when needed. The area under the sedation score-time curve for visual analogue scale (AUC_{VAS30}) was calculated for the first 30 min after treatment using the trapezoidal method. Repeated ANOVA, Mann–Whitney *U* test and Fisher's exact test were used for parametric, non-parametric and dichotomous data. Heart rate was significantly higher from 10 to 40 min with MB-MK than with MB. AUC_{VAS30} was significantly higher after MB-MK. More dogs treated with MB-MK required additional sedation after 30 min, but fewer needed atipamezole for reversal compared with MB. Plasma concentrations of both medetomidine and butorphanol were higher after MB-MK. All procedures were successfully completed. MK-467 alleviated the bradycardia, intensified the early stage sedation and shortened its duration in healthy dogs that received IM medetomidine-butorphanol.

Introduction

The α2-adrenoceptor agonists medetomidine and dexmedetomidine produce reliable sedation and some degree of analgesia, permitting minor procedures to be performed in clinical veterinary practice (Scheinin and MacDonald, 1989; Murrell and Hellebrekers, 2005). Butorphanol is a synthetic opioid that is frequently used with medetomidine to enhance the quality of sedation in dogs (Pypendop et al., 1996; Kuo and Keegan, 2004). However, all α2-adrenoceptor agonists have adverse effects, mainly related to depression of the cardiovascular system. Specifically, α2-adrenoceptor agonists induce vasoconstriction (Bloor et al., 1992), followed by marked baroreflex-mediated bradycardia (Pypendop and Verstegen, 1998). The bradycardia is associated with pronounced decreases in cardiac output and oxygen delivery (Bloor et al., 1992; Pypendop and Verstegen, 1998), an outcome that challenges the usefulness of these drugs.

Although the beneficial effects (i.e. sedation and analgesia) of α2-adrenoceptor agonists are produced at the level of the central nervous system (CNS), activation of peripheral α2-adrenoceptors located within vascular smooth muscle leads to the initial vasoconstriction and related cardiovascular effects (Clough and Hatton, 1981; Horn et al., 1982). In view of this, MK-467 (vatinoxan; L-659'066), a peripherally acting α2-adrenoceptor antagonist (Clineschmidt et al., 1988), has been investigated for its ability to prevent or attenuate the negative impact of dexmedetomidine and medetomidine in dogs (Pagel et al., 1998; Enouri et al., 2008; Honkavaara et al., 2008; Honkavaara et al., 2011).

Only a small proportion of MK-467 crosses the blood–brain barrier into the mammalian CNS (Clineschmidt et al., 1988). Thus,

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the pharmacodynamic actions of MK-467 are limited to tissues and organs outside the blood–brain barrier. Several studies have demonstrated that MK-467 is able to prevent cardiovascular depression in dogs (Pagel et al., 1998; Enouri et al., 2008; Honkavaara et al., 2008, 2011) without substantially altering the sedation elicited by dexmedetomidine and medetomidine (Honkavaara et al., 2008; Restitutti et al., 2011, 2017). It has also been shown that concomitant administration of MK-467 attenuates the cardiovascular effects of a medetomidine–butorphanol combination when both are given by intramuscular (IM) injection in the same syringe (Salla et al., 2014). Furthermore, an increase in the absorption rate of medetomidine, when combined with MK-467 for IM administration, has been reported (Restitutti et al., 2017).

To date, studies on MK-467 in dogs have been performed using laboratory beagles under controlled, experimental conditions. Hence, our aim was to investigate the effects of MK-467 on sedation and bradycardia expected after IM administration of medetomidine and butorphanol in healthy dogs of various breeds in a clinical environment. We hypothesised that MK-467, when co-administered IM with medetomidine and butorphanol, would attenuate bradycardia without impairing the sedative action of this commonly used combination.

Materials and methods

Animals

After receiving approval from the National Animal Experimental Board of Finland (approval number ESAVI/6082/04.10.07/2016, Date of approval 8th October 2016), the study was performed at the Veterinary Teaching Hospital, Faculty of Veterinary Medicine, University of Helsinki, Finland. The target population was client owned dogs that required sedation for non-invasive radiographic imaging. Inclusion criteria were weight ≥5 kg, age from 3 months to 10 years and American Society of Anesthesiologists (ASA) classification I and II. Exclusion criteria were breed-related contraindication for deep sedation (e.g. brachycephalic syndrome), systemic disease or medications affecting the CNS. Informed consent was obtained from the owners. Most of the dogs enrolled in the study were scheduled for radiographic imaging required by the Finnish Kennel Club Health Programme for the screening of canine genetic diseases and defects.

Experimental design

In a randomised, complete, block design, animals were assigned to receive one of two treatments: (1) 0.5 mg/m^2 medetomidine HCl + 0.1 mg/kg butorphanol tartrate (MB); or (2) 0.5 mg/m^2 medetomidine HCl + 0.1 mg/kg butorphanol tartrate + 10 mg/m^2 MK-467 HCl (MB-MK). The body surface area was calculated using the following formula: body surface area (m^2) = 10.1 × (weight in kg)$^{2/3}$ × 10^{-2} (White and Kearney, 2014; Pypendop and Jones, 2015). The dose of medetomidine HCl (0.5 mg/m^2) was equivalent to a dose of 29.5 μg/kg for a 5 kg dog and 11.7 μg/kg for an 80 kg dog. A solution containing 0.5 mg/mL medetomidine HCl for the MB treatment and a solution containing 0.5 mg/mL medetomidine HCl and 10 mg/mL MK-467 HCl (Vetcare Oy; Recipharm) was used for the MB-MK-treatment. Butorphanol (Torpudor 10 mg/mL, Richter Pharma AG) was drawn up separately and mixed with the solution containing medetomidine before administration. The end volume of the injectable solution in both treatments was 0.03 to 0.07 mL/kg (0.57 mL for a 10 kg dog), depending on the weight. Randomisation (Microsoft Office Excel) into treatment groups was performed in blocks for breed (Retrievers, Shepherds, Spitzs and the group 'Other breeds') and weight (small dogs 5–10 kg, medium size dogs 11–30 kg and large dogs >31 kg) to ensure relatively homogeneous populations between treatments. Treatments were administered IM into the gluteal muscles.

Ten minutes after drug injection, a catheter was inserted in a cephalic vein aseptically and blood was drawn into tubes containing ethylene diamine tetra-acetic acid (EDTA) for plasma drug concentration analyses and complete blood counts, and into a serum tube for basic serum chemistry. Blood samples obtained later than 20 min after drug injection were excluded from the plasma drug concentration data. The total volume harvested was <10 mL, representing no more than 3% of the total blood volume of a 5 kg dog. Plasma was separated by centrifugation at 2300 *g* for 10 min within 30 min after collection and stored at −20 °C until analysis for medetomidine, butorphanol and MK-467 concentrations.

Oxygen was supplemented with a loose mask at 2–4 L/min according to the dog's size. Prior to treatment administration, heart rate (HR) was assessed by auscultation, respiratory rate was assessed by observation of thoracic movements, colour of the mucous membranes was assessed by direct observation and the level of sedation was scored. The evaluations were repeated at 5 min after treatment and thereafter at 10 min intervals. Rectal temperatures were measured prior to treatment administration and at every 30 min. Dogs were passively insulated with blankets; if the body temperature decreased <37 °C, they were warmed actively by a convective temperature management system (Bair-Hugger, 3M).

The primary investigator who assessed the sedation was blinded to the treatment. A second investigator administered the treatments and recorded the HRs and other clinical variables. Sedation was determined using a visual analogue scale (VAS) from 0 to 100, where 0 represents no sedation and 100 represents the animal in lateral recumbency, unresponsive to a loud hand clap. The 'area under the sedation score time' curve for VAS was calculated for the first 30 min after treatment (AUC_{VAS30}) using the trapezoidal method. 'Head down time' was recorded as the time when the dog had become recumbent and did not react to the hand clap. If the level of sedation was inadequate for performing the radiographic imaging, as judged by the blinded investigator, 50% of the initial medetomidine dose (without butorphanol and MK-467) was administered IM. Treatment failure was defined as insufficient sedation after the additional medetomidine.

The duration of required sedation was recorded as the time from the IM injection until the radiographic imaging was concluded. After successful completion of the procedure, the blinded investigator administered 0.625 mg/m^2 atipamezole IM (37 μg/kg for a 5 kg dog; Alzane 5 mg/mL, Laboratorios SYVA S. A.U.) if the dog was not able to stand or walk. If the dog was not able to stand on its own after the first dose, the same dose was re-administered 10 min later. The evaluations were continued as described above until the animal was standing. The owner was interviewed by telephone the following day regarding the overall behaviour of the dog: (1) was the dog more lethargic than normal in the evening after sedation; (2) was there anything else out of the ordinary; and (3) were there any changes in appetite, faeces or behaviour? Owners were blinded to the treatment until the end of the telephone call.

Analytical methods

Concentrations of medetomidine, butorphanol and MK-467 in plasma were measured using liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS; Waters Acquity UPLC + Waters TQ-S triple quadrupole MS). After precipitation of 100 μL plasma samples in a 96-well precipitation plate (Waters Sirocco Waters) with 200 μL acetonitrile containing 20 ng/mL chlorpromazine as an internal standard, the plasma supernatants were transferred to new 96-well plates and a 50 μL aliquot was transferred to another 96-well plate and diluted 1:10 in 20% aqueous acetonitrile prior to analysis. Diluted and undiluted samples were analysed. Reference standards were prepared by 'spiking' blank dog plasma with the analytes, producing final concentrations in the range 0.02–20,000 ng/mL. The linear calibration ranges were fitted as 0.2–500 ng/mL for undiluted butorphanol, 0.2–2000 ng/mL for diluted medetomidine and 0.5–2000 ng/mL for undiluted MK-467. The quality control samples were within 94–116% of the nominal concentrations.

Statistical analysis

A power analysis, based on mean HRs of 40 (MB) and 60 (MB-MK) beats per min (bpm), with a standard deviation of 15 bpm, suggested that 20 dogs per group was required with a power of 80% and α level of 0.05. The Shapiro–Wilk test was used to evaluate the normality of data distributions. Heart and respiratory rates were evaluated by analysis of variance (ANOVA; general linear model), where time was a within-subject factor and treatment was a between-subject factor. A *t* test with the Holm–Bonferroni post-hoc correction was used for comparisons between treatments and against baseline. The independent samples *t* test was performed on plasma drug concentrations and time for 'head down'. Areas under the curve (AUC_{VAS30}) were compared using the Mann–Whitney *U* test. VAS and pale mucous membranes were compared between the two treatments at each time point using the Mann–Whitney *U* test and against baseline within each treatment using the related samples Friedman's two-way ANOVA by ranks. The Holm–Bonferroni correction was used with both comparisons. The need for additional medetomidine or atipamezole, presence of loose faeces, lethargy and decreased appetite were compared using the two-sided Fischer's exact test. Analyses were computed using SPSS Statistics version 24.0 for Windows (IBM). *P* values <0.05 were considered to be statistically significant.

Results

The MB group contained 29 dogs and the MB-MK group contained 27 dogs (Table 1). None of the dogs had pertinent alterations in haematology or serum chemistry considered to be consequential to the investigated outcomes. All the procedures were completed successfully and no treatment failures occurred in either group. Side effects, considered to be minor, are reported in Table 2.

Table 1
Characteristics of 56 dogs undergoing sedation with either MB ($n = 29$) or MB-MK ($n = 27$) for radiography.

	MB	*n*	MB-MK	*n*
Weight (kg)[a]	18.6 (6.3–42.0)		24.6 (8.8–71.0)	
Age (years)[a]	2.3 (1.1–8.8)		2.9 (1.1–9.4)	
Sex	Male	12	Male	9
	Female	17	Female	18
Breed	German shepherd	4	German shepherd	5
	Border collie	3	Flat coat retriever	2
	Giant schnauzer	3	Lapphund	2
	Golden retriever	2	Lapponian herder	2
	Lapphund	2	Pyrenean mastiff	2
	Lapponian herder	2	Whippet	2
	Mudi	2	American Staffordshire bull terrier	1
	Mixed breed	2	Australian shepherd	1
	Bohemian shepherd	1	Bassett hound	1
	Cairn terrier	1	Bedlington terrier	1
	Cirneco delletna	1	Border collie	1
	Cocker spaniel	1	Cairn terrier	1
	Flat coated retriever	1	Cocker spaniel	1
	Miniature schnauzer	1	Entlebucher sennenhund	1
	Podenco	1	Giant schnauzer	1
	Schweizer laufhund	1	Golden retriever	1
	Whippet	1	Mixed breed	1
			Norwegian elkhound	1

MB, 0.5 mg/m^2 medetomidine + 0.1 mg/kg butorphanol; MB-MK, 0.5 mg/m^2 medetomidine + 10 mg/m^2 MK–467 + 0.1 mg/kg butorphanol.
The group size of a breed for each treatment is expressed as the number of individuals of that breed.
[a] Median and range in curved brackets. No significant differences were detected between groups in weight, age or sex.

HRs were reduced from baseline after both treatments; however, HR was significantly higher in the MB-MK group than in the MB group (Fig. 1). HRs were reported until 40 min; at that time point, two dogs were missing from each group, representing the end of the procedure for one dog in each group and the requirement for additional sedation in one dog in each group. The lowest HRs detected after additional treatment with medetomidine were 28 bpm in the MB group ($n = 1$) and 34 bpm in the MB-MK group ($n = 7$). One dog in the MB group had an increased HR after drug administration (up to 148 bpm); this was considered to be an outlier the HR data for this dog were excluded from Fig. 1 and from the statistical analyses.

VAS and AUC_{VAS30} are shown in Table 3. In the MB-MK group, more dogs required additional sedation after 30 min than in the MB group. In addition, fewer dogs in the MB-MK group required administration of atipamezole (Table 2). Respiratory rates decreased after both treatments, with no significant difference between groups. The lowest respiratory rates were detected at 20–30 min, with medians of 8 and 10 breaths per min in the MB-MK and MB groups, respectively. None of the dogs had a rectal temperature below 37 °C. Due to technical problems there were many missing blood pressure readings (data not analysed nor shown).

Plasma concentrations of both medetomidine and butorphanol were significantly higher in the MB-MK group in samples collected 11–18 min after drug injection (Table 2). 'Head down' time, mucous membrane colour, duration of required sedation, lethargy, loose faeces, decrease in appetite, number of blood samples analysed and sampling time are shown in Table 2.

Discussion

The findings of this study, using a population of healthy dogs in a clinical setting, indicate that administration of MK-467 IM concomitantly with medetomidine and butorphanol alleviates medetomidine-related bradycardia. Profound bradycardia (approximately 40 bpm) was detected in dogs treated with medetomidine and butorphanol (MB group). The HR was also low in dogs treated with medetomidine, butorphanol and MK-467 (MB-MK group; mean HR approximately 60 bpm). However, similar or even lower HRs have been detected in untreated, healthy sleeping dogs; nightly HRs ~60–70 bpm have been reported in beagle dogs (Nolan et al., 2004; Honkavaara et al., 2008). Moreover, in healthy, adult, pet dogs, minimum HRs of 17–46 bpm have been detected on ambulatory electrocardiography (Hall et al., 1991) and, in a more recent study, the mean of the minimum HRs was also <50 bpm (Cruz Aleixo et al., 2017). In our study, HR was significantly lower than baseline in the MB-MK group, which suggests that MK-467 did not override the central component of the bradycardic action of α2-agonists (Savola, 1986), although it was presumed to have been able to alleviate the baroreflex-mediated bradycardia caused by peripheral α2-adrenoceptor activation.

The present results should not be over-interpreted, since we did not show that cardiac output or oxygen delivery were improved by the addition of MK-467. However, in experimental canine studies,

Table 2
Results for 56 dogs undergoing sedation with either MB ($n = 29$) or MB-MK ($n = 27$) for radiography.

	MB	MB-MK	*P* value
Head down (s)[a]	297.5 ± 74.3	241.4 ± 77.8	0.012
Pale mucous membranes[b]	10	3	0.058
Additional medetomidine[b] (min[a])	1 (30)	7 (53 ± 10)	0.023
Atipamezole administration[b]	26	12	<0.001
Duration of required sedation[c] (min[a])	66 ± 14.5 (30–94)	66 ± 19 (42–111)	
Lethargy[b]	26	17	0.221
Loose faeces[b]	7	9	0.558
Decrease in appetite[b]	2	3	0.664
Blood sample analysed[b]	23	25	
Blood sampling time (min)[c,d]	13 (11–15)	13.5 (12–18)	0.36
Medetomidine (ng/mL[a])	9 ± 3	14 ± 4	<0.001
Butorphanol (ng/mL[a])	16 ± 7	35 ± 15	<0.001
MK-467 (ng/mL[a])		607 ± 204	

MB, 0.5 mg/m^2 medetomidine + 0.1 mg/kg butorphanol; MB-MK, 0.5 mg/m^2 medetomidine + 10 mg/m^2 MK–467 + 0.1 mg/kg butorphanol.
Lethargy, loose faeces and decrease in appetite reported by owners.
One dog in both groups received additional medetomidine and one dog in both groups received additional atipamezole.
[a] Mean ± standard deviation.
[b] Number of dogs.
[c] Range in curved brackets.
[d] Median.

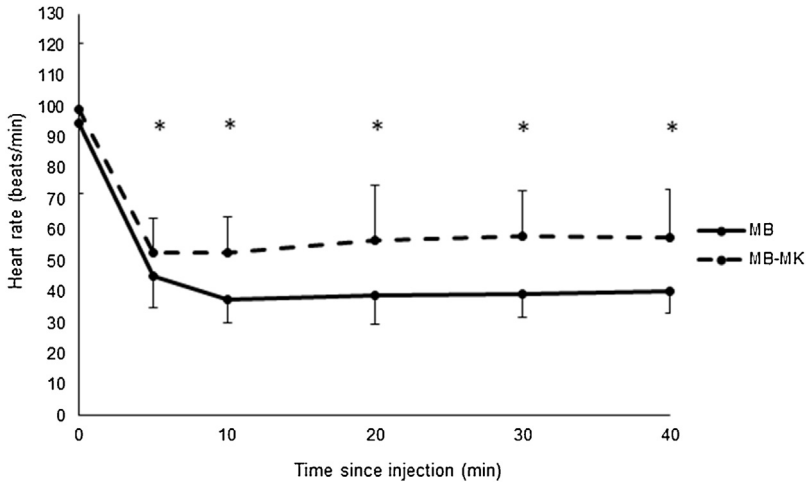

Fig. 1. Heart rates until 40 min after injection for dogs that did not receive additional medetomidine or atipamezole. *Significant difference between treatments.

Table 3
Visual analogue sedation score (0–100) and the area under the sedation score time curve (AUC) for visual analogue scale (VAS) for the first 30 min (AUC_{VAS30}).

Time point (min)	MB	MB-MK
0	0 (0–0) $n = 29$	0 (0–0) $n = 27$
5	58 (9–86) $n = 28$	64* (21–100) $n = 27$*
10	96 (31–100) $n = 27$*	100 (51–100) $n = 27$*
20	100 (82–100) $n = 28$*	100 (78–100) $n = 27$*
30	100 (83–100) $n = 28$*	100 (71–100) $n = 27$*
40	100 (90–100) $n = 26$*	100 (14–100) $n = 25$*
AUC_{VAS30}	2445 (1855–2585)†	2555 (1868–2750)†

MB, 0.5 mg/m^2 medetomidine + 0.1 mg/kg butorphanol; MB-MK, 0.5 mg/m^2 medetomidine + 10 mg/m^2 MK-467 + 0.1 mg/kg butorphanol.
Data are reported as median (range).
* Significant difference from baseline.
† Significant difference between treatments.

the alleviation of bradycardia by MK-467 has been associated with improvement of cardiac output (Honkavaara et al., 2011; Salla et al., 2014). The lack of blood pressure data in our study is a major limitation; blood pressure was monitored non-invasively and blood pressure measurements could not be carried out systematically at the prescribed same time points, nor using the same artery, because the clinical priority was to avoid excessive interference with the radiological exams. Therefore, we did not consider the data to be reliable and further studies using clinical cases are needed.

The onset of sedation appeared to be faster in the MB-MK group and, initially, was deeper than in the MB group. The 'head-down' time was significantly shorter in the MB-MK group and we detected a deeper overall sedation during the first 30 min. Subsequently, dogs in the MB-MK group were more alert than dogs in the MB group, since more additional medetomidine and less atipamezole were required. Thus, the use of MK-467 can be considered advantageous, especially if short, intense, sedation is required. If additional medetomidine was needed, medetomidine alone was given to dogs in both groups, since no studies have been performed on the effects of repeated doses of MK-467 in sedated dogs. Since the need for additional sedation arose after a mean of 52 min in dogs in the MB-MK group, the duration and magnitude of the sedative effect of medetomidine and butorphanol combined with MK-467 could provide sufficient sedation to complete a minor non-invasive procedure. The quality and level of sedation induced by medetomidine in our study probably were improved by butorphanol, independent of MK-467, in accordance with that reported previously (Pypendop et al., 1996; Ko et al., 2000). Conversely, the effects of MK-467 on the plasma concentration profile of medetomidine and butorphanol apparently also affected the depth of sedation.

The interactions between α2-adrenoceptors and their antagonists start at the site of the extravascular injection; MK-467 enhances the IM absorption of medetomidine, probably by preventing local vasoconstriction caused by medetomidine (Restitutti et al., 2017) and it also appears to affect the absorption of other co-administered sedatives (Kallio-Kujala et al., 2017). In our study, plasma medetomidine and butorphanol concentrations were significantly higher in the MB-MK group than in the MB group. The plasma sample was collected approximately 14 min after the injection, when we expected to detect a clear difference between the treatments based on our previous findings (Kallio-Kujala et al., 2017; Restitutti et al., 2017). Furthermore, Restitutti et al. (2017) reported that the time-concentration curves of dexmedetomidine intersected at approximately 30 min; the plasma concentration of medetomidine was higher in the presence of MK-467 before the 30 min time point, whereas later it was higher in dogs that had received medetomidine alone IM. These effects of MK-467 on the plasma concentration profiles of medetomidine and butorphanol probably explain both the deeper initial sedation observed in the MB-MK group and the later lighter plane of sedation in the MB-MK group when compared with the MB group.

The most frequent side effects after sedation in both groups were lethargy and loose faeces during the evening after the examination. All dogs that had loose faeces had received one or both of the α2-adrenoceptor antagonists MK-467 and/or atipamezole. Atipamezole restores intestinal motility after α2-adrenoceptor agonist-induced sedation and induces defaecation in dogs (Maugeri et al., 1994). Moreover, frequent defaecation after administration of MK-467 has been reported in horses (DeVries et al., 2016). Therefore instead of giving atipamezole in one single dose, we administered two equal (0.625 mg/m^2) smaller doses if needed, to reduce the risk of intestinal hypermotility, especially in the presence of MK-467, but still to have the desired effect of reversing the sedation. Honkavaara et al. (2008) administered atipamezole 50 μg/kg (1.25 mg/m^2 for a 16 kg dog) to reverse sedation induced by IV dexmedetomidine and MK-467.

Conclusions

MK-467 alleviates the bradycardia induced by medetomidine in dogs in a clinical setting, and provides reliable sedation for short

term clinical procedures, such as diagnostic imaging, when it is combined with IM medetomidine and butorphanol in healthy dogs. In addition, MK-467 increases the early stage plasma concentration of both medetomidine and butorphanol when administrated IM in the same syringe and results in deeper initial sedation with shorter duration.

Conflict of interest statement

None of the authors of this paper have a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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