Article

Behavioral response and cost comparison of manual *versus* pharmacologic restraint protocols in healthy dogs

Michele Barletta, Marc Raffe

Abstract — Although sedatives are routinely administered to dogs for diagnostic and minimally invasive procedures, manual restraint is often used. The study compared intra-procedural behavioral response, scored on a 100-point, visual analog scale, and cost of restraint in healthy dogs given 1 of 5 treatments: manual restraint, dexmedetomidine at 125 μg/m^2 (Dex 125) or 375 μg/m^2 (Dex 375), Dex 125 plus butorphanol at 0.4 mg/kg (Dex 125 + Bu), or Dex 375 plus butorphanol at 0.4 mg/kg (Dex 375 + Bu). Mean behavioral response scores in dogs declined from baseline in the manual restraint group and improved in a linear fashion in the group order Dex 125, Dex 375, Dex 125 + Bu, and Dex 375 + Bu. Dexmedetomidine at 375 μg/m^2 or at 125 μg/m^2 or at 375 μg/m^2 in combination with butorphanol produced the best intra-procedural behavioral response. The cost of sedative drugs was offset by the opportunity cost of diverting personnel from revenue-generating activity to manual restraint.

Résumé — Réaction comportementale et comparaison du coût des protocoles de contention manuelle par rapport aux protocoles de retenue pharmacologiques chez des chiens en santé. Même si des sédatifs sont régulièrement administrés aux chiens pour des procédures diagnostiques ou minimalement invasives, la contention manuelle est souvent utilisée. L'étude a comparé la réaction comportementale durant la procédure, évaluée sur une échelle analogue visuelle de 100 points, et le coût de la retenue chez des chiens en santé auxquels on a administré l'un de 5 traitements : la contetnion manuelle, la dexmédétomidine à 125 μg/m^2 (Dex 125) ou à 375 μg/m^2 (Dex 375), la Dex 125 et du butorphanol à 0,4 mg/kg (Dex 125 + Bu) ou la Dex 375 et du butorphanol à 0,4 mg/kg (Dex 375 + Bu). Les notes moyennes de réaction comportementale chez les chiens ont chuté de la valeur de base dans le groupe de contention manuelle et elles se sont améliorées de façon linéaire dans l'ordre des groupes Dex 125, Dex 375, Dex 125 + Bu et Dex 375 + Bu. La dexmédétomidine à 375 μg/m^2 ou à 125 μg/m^2 ou à 375 μg/m^2 en combinaison avec du butorphanol a produit la meilleure réaction comportementale pendant la procédure. Le coût des sédatifs a été compensé par le coût découlant de l'affectation du personnel à des activités produisant des revenus au lieu de la contention manuelle.

(Traduit par Isabelle Vallières)

Can Vet J 2016;57:258–264

Introduction

Veterinarians commonly use sedation and analgesia agents to facilitate minimally invasive outpatient procedures of short duration, the most common type of diagnostic and therapeutic cases encountered in companion animal practice. For these types of procedures, α2-adrenoceptor agonists have a well-established role in canine and feline sedation and pre-anesthesia. The advantages of α2-agonsists include the convenience of injectable administration, a rapid dose-dependent response (1,2), a self-limiting physiological ceiling effect (1,3,4), compatibility with other classes of neurotropic drugs, including an additive or dose-sparing effect when used in multi-modal sedation-analgesia-anesthesia protocols (5–11), rapid reversibility with injectable α-2 antagonist such as atipamezole (7), and availability as a non-scheduled drug approved for use in dogs ≥ 16 wk of age and cats ≥ 12 wk of age. The main disadvantage of this class of drugs is their cardiovascular effects, resulting in bradycardia, bradyarrhythmias, and reduction of cardiac output. For this reason, appropriate patient selection is paramount and administration of α2-agonists should be avoided in sick or unstable animals and those with cardiovascular deficiencies (12).

Dexmedetomidine is the newest α2-agonist approved for use in companion animal medicine. Dexmedetomidine is the active enantiomer of the racemic compound medetomidine, which combines dexmedetomidine and its inactive stereoisomer levomedetomidine (4,11,13,14). Because it is synthesized

College of Veterinary Medicine, Department of Large Animal Medicine, 501 DW Brooks Drive, University of Georgia, Athens, Georgia 30602, USA (Barletta); Outcomes Research, Zoetis Inc, 100 Campus Drive, Florham Park, New Jersey 07932, USA (Raffe).

Address all correspondence to Dr. Michele Barletta; e-mail: barletta03@gmail.com

without levomedetomidine, dexmedetomidine has improved potency *versus* medetomidine (4,15). Dexmedetomidine has a well-established role in clinical medicine; indeed, it has not only found a place in veterinary practice but was first approved by the FDA in 1999 as a safe and effective short-term sedative and analgesic for humans (1).

The physiologic effects of dexmedetomidine in dogs and cats have been reported in previous studies (4,7,16–18), and its application as a stand-alone sedative or in pre-anesthetic protocols has been described (5,9–11,15,19,20). However, no study has compared the resource utilization and economic impact of dexmedetomidine and dexmedetomidine-opioid combinations compared to manual restraint. The objective of this study was to compare the procedural efficacy and economic impact of dexmedetomidine alone or in combination with butorphanol *versus* manual restraint for common canine diagnostic and therapeutic procedures performed in a limited number of dogs presented at the University of Minnesota Veterinary Medical Center (VMC). Procedural efficacy was measured by assessing patient behavior and cooperation. The economic impact was measured by assessing drug and labor costs and opportunity cost. Opportunity cost considers the value of resources diverted from a revenue-generating activity to an alternative choice of lesser value. In this study, opportunity cost was the value of excess personnel time used for manual restraint in lieu of revenue-generating clinical or client-related activity. Examples of the impact of opportunity cost on healthcare economics have been previously described (21,22).

Materials and methods

Animals

Owners were required to sign a consent form prior to enrollment of their dogs in the study. The project was approved by the University of Minnesota Institutional Animal Care and Use Committee to confirm humane animal treatment. Client-owned dogs of various breeds and older than 6 mo of age presented at the University of Minnesota VMC were enrolled in this study. All dogs weighed more than 2.25 kg and were clinically healthy. Exclusion criteria included an American Society of Anesthesiologists (ASA) physical status score greater than or equal to 3, known hypersensitivity to the drug classes used in the study, and treatment with preanesthetic or anesthetic drugs, sympathomimetic amines, anticholinergics, tranquilizers, sedatives, central nervous system (CNS) modifiers, or analgesics except for NSAIDs within 7 d prior to presentation. If a minimally invasive surgical procedure was performed (e.g., skin biopsy) an infiltration of local anesthetic was allowed. Also excluded were dogs that were considered intractable or aggressive. All enrolled dogs were given a physical examination and assigned an ASA score, identified with a medical collar containing a unique case number, and weighed for purposes of dose calculation within 3 h prior to sedation. Body temperature and heart and respiratory rates were determined within 1 h prior to sedation. Initial examination, ASA assessment, and study observations were conducted by the same board-certified anesthesiologist or third-year anesthesia resident prior to treatment.

Study design

Fifty female and 50 male dogs were enrolled in the study. Within gender, dogs were blocked into groups of 5 as they entered the study. Each of the dogs in a gender block was randomly assigned to 1 of 5 treatment groups (10 male and 10 female dogs per group): manual restraint, dexmedetomidine (Dexdomitor; Zoetis, Florham Park, New Jersey, USA), 125 $\mu g/m^2$ [approximately 4.2 μg/kg body weight (BW) for a 30-kg dog] (Dex 125), dexmedetomidine 375 $\mu g/m^2$ (approximately 12.5 μg/kg BW for a 30-kg dog) (Dex 375), dexmedetomidine 125 $\mu g/m^2$ and butorphanol (Torbugesic; Zoetis) 0.4 mg/kg (Dex 125 + Bu), or dexmedetomidine 375 $\mu g/m^2$ and butorphanol 0.4 mg/kg (Dex 375 + Bu). Dexmedetomidine and butorphanol were administered by IM injection in the quadriceps femoris muscle 20 min before the medical procedure was started. Each dog's temperature, heart rate, and respiratory rate were recorded when the procedure was initiated and every 10 min thereafter until completion. Sedation reversal with IM atipamezole (Antisedan; Zoetis) was performed following completion of the procedure for dogs treated with dexmedetomidine. The dose of atipamezole was 10 times the corresponding dose of dexmedetomidine, which was 1.25 mg/m^2 (approximately 42 μg/kg BW for a 30-kg dog) and 3.75 mg/m^2 (approximately 125 μg/kg BW for a 30-kg dog) for dogs receiving 125 $\mu g/m^2$ and 375 $\mu g/m^2$ of dexmedetomidine, respectively.

Two intra-procedural variables, patient behavior and patient cooperation, were scored on a 100-point (10-cm) visual analog scale (VAS). Patient behavior was defined as the dog's demeanor without human intervention. Patient cooperation was defined as the dog's response to human contact and tolerance of the medical procedure. Patient cooperation was assessed in 3 phases in which the animal was observed for a minimum of 15 s for each evaluation. During phase 1 the score was assigned when the dog was undisturbed, in phase 2 when approached and addressed verbally to encourage movement, and in phase 3 during physical contact. The assessment considered the dog's posture, basal activity level, response to sound, and muscle relaxation. A cooperation score was assigned on a VAS from non-cooperative (0) to completely cooperative (100) at baseline just before the treatment was administered (0 time point), 20 min later when the medical procedure was initiated, and at 10-min intervals thereafter until completion of the procedure. The patient's behavior was similarly scored based on a single, 15-second observation at the same time points used to assess patient cooperation. Visual analog scale scores for behavior ranged from agitated (VAS = 0) to completely sedate (VAS = 100). Observers were instructed to use consistent techniques in approaching test dogs, using verbal cues, and methods of palpation and examination.

In addition to the subjective assessments of patient cooperation and behavior, objective parameters that were measured for each dog were the number of personnel and contact time required for restraint. Restraint contact time was considered to be the amount of time a person was in physical contact with the dog solely for purposes of restraint. The person monitoring the dogs during the procedure was a trained anesthesia technician and was aware of the treatment administered. This was necessary to ensure optimal patient care. The person scoring behavior,

Table 1. Procedures performed per group

Restraint protocol[a]	Procedure performed: Radiographs alone	Radiographs + arthrocentesis	Radiographs + bandage change	Radiographs + aspirate biopsy	Other procedures	Total
Manual	13	1	1	—	3	18
Dex 125	12	2	—	—	3	17
Dex 375	16	—	—	—	1	17
Dex 125 + Bu	16	1	—	1	1	19
Dex 375 + Bu	14	3	—	—	2	19
Total	71	7	1	1	10	90

[a] Dex 125 and Dex 375 — dexmedetomidine in μg/m² given IM at 0 min. Bu — butorphanol at 0.4 mg/kg given IM at 0 min.

Table 2. Comparison of opportunity cost for different restraint options

Restraint protocol[a]	1. Mean number of personnel required for restraint (range)	2. Mean contact time (min) required for restraint (range)	3. Mean personnel-min required for restraint (col 1 × col 2)	4. Mean opportunity cost ($) (col 3 × $1.10)[b]	5. Mean opportunity cost ($) *versus* Dex 375 + Bu (col 4 − 6.66)
Manual	2.4 (1–4)	18.1 (10–40)	43.44	47.78	41.12
Dex 125	2.2 (1–4)	16.2 (5.3–30)	35.64	39.20	32.54
Dex 375	1.4 (0–3)	7.9 (0–17.5)	11.06	12.17	5.51
Dex 125 + Bu	1.2 (0–3)	6.9 (0–17.0)	8.28	9.11	2.45
Dex 375 + Bu	1.1 (0–3)	5.5 (0–16.7)	6.05	6.66	—

[a] Dex 125 and Dex 375 — dexmedetomidine in μg/m² given IM at 0 min. Bu — butorphanol at 0.4 mg/kg given IM at 0 min.
[b] See Appendix for calculation of opportunity cost revenue per min.

cooperation, number of people required, and whether or not the level of sedation was sufficient to complete the procedure was blinded to the treatment.

An economic analysis was performed for each restraint protocol to determine the average per-procedure cost for labor and drugs plus the opportunity cost associated with each restraint option. The bases for the labor cost-per-minute for purposes of restraint ($0.24) and opportunity cost-per-minute ($1.10) are shown in the Appendix. Arithmetic means were calculated for the following outcomes: patient cooperation and behavior scores for each treatment option and time point, number of personnel per procedure, and contact time required for restraint, and per-procedure labor cost for restraint and opportunity cost.

Results

Ten dogs were removed from the study due to protocol deviations (n = 1 each in the Dex 125 and Dex 375 + Bu groups) or for failure to initiate the medical procedure due to inadequate restraint (n = 2 in the manual restraint, 2 in the Dex 125, 3 in the Dex 375, and 1 in the Dex 125 + Bu groups). All 8 animals showing inadequate restraint were removed within the first minute from the beginning of the study; therefore, these data were not included in the cost analysis. Final enrollment by group was 18 for manual restraint, 17 each for the groups given dexmedetomidine alone, and 19 each for the groups given combination treatment with dexmedetomidine and butorphanol. All dogs were between 7 mo and 13 y of age and weighed 29 ± 14 kg (mean ± standard deviation). A D'Agostino-Pearson test demonstrated that body weight was normally distributed. Procedures performed on study dogs included radiographs alone (n = 71), radiographs plus arthrocentesis (n = 7), radiographs plus bandage change (n =1), and radiographs plus aspirate biopsy (n = 1). Other procedures (n = 10) included minor surgery (skin biopsy, corneal debridement, small skin mass removal), ultrasound examination, and urinary catheterization (Table 1).

Dogs controlled manually required the largest mean number of personnel (2.4) and the longest mean contact time (18.1 min) for physical restraint compared to all other groups (Table 2). A minimum of 1 and as many as 4 people were required for manual restraint in some cases *versus* a maximum of 3 people for dogs managed pharmacologically. No additional personnel were required for restraint of some dogs in the Dex 375, Dex 125 + Bu, or Dex 375 + Bu groups. The mean personnel and contact time parameters both declined in a linear fashion for groups Dex 125 (2.2 persons, 16.2 min), Dex 375 (1.4 persons, 7.9 min), Dex 125 + Bu (1.2 persons, 6.9 min), and Dex 375 + Bu (1.1 persons, 5.5 min).

Mean behavior and cooperation scores for dogs undergoing manual restraint decreased from their baseline VAS at the 20- and 30-min time points (Tables 2 and 3). Mean cooperation scores decreased to a greater extent than the mean behavior scores. The mean cooperation score for dogs receiving manual restraint declined by 16.7 points at 20 min, then declined further by 24.9 points at the 30-minute time point, indicating a general deterioration in cooperation as the procedure progressed. Improvements from baseline in mean behavior and cooperation scores in manual restraint cases tended to be minimal, although a 33-point improvement was observed in 1 dog at the 20-min interval. In some individual cases, the decline in behavior and cooperation in manually restrained dogs was precipitous. For example, individual behavior scores declined from baseline score by as much as 65 points at 20 min and individual cooperation scores declined from the VAS baseline by as much as 60 points at 20 min and 82 points at 30 min. Most manual restraint cases

Table 3. Mean change from baseline in intra-procedural behavior scores of dogs following manual or pharmacologic restraint

	Post-treatment interval (min) and mean deviation (plus/minus) from baseline score of 0 as midpoint on a 100-point VAS[b]				
Restraint protocol[a]	20	30	40	50	60
Manual restraint (*n* = 18)	−9.8 (−65/4) *n* = 18	−9.0 (−36/2) *n* = 7	0 (−1/1) *n* = 2	NA *n* = 0	NA *n* = 0
Dex 125 (*n* = 17)	−0.7 (−41/35) *n* = 17	5.9 (−43/56) *n* = 14	23.2 (−5/66) *n* = 9	30.7 (−12/76) *n* = 6	19.7 (−22/77) *n* = 3
Dex 375 (*n* = 17)	22.1 (−21/78) *n* = 17	28.2 (−32/83) *n* = 16	20.1 (−12/45) *n* = 9	−20.0 *n* = 1	NA *n* = 0
Dex 125 + Bu (*n* =19)	30.2 (−23/76) *n* = 19	33.1 (−27/75) *n* = 19	37.9 (−4/66) *n* = 13	47.2 (27/83) *n* = 6	47.0 (22/87) *n* = 4
Dex 375 + Bu (*n* = 19)	34.6 (−19/55) *n* = 19	41.4 (14/69) *n* = 19	40.3 (8/69) *n* = 13	53.2 (39/71) *n* = 5	49.3 (41/57) *n* = 4

[a] Dex 125 and Dex 375 — dexmedetomidine in μg/m² given IM at 0 min. Bu — butorphanol at 0.4 mg/kg given IM at 0 min.
[b] Visual analog scale (VAS) is from agitated (0) to sedate (100), i.e., higher values indicate more controlled behavior.
NA — not applicable.

(11/18) were completed in less than 30 min, and all but 2 cases were completed in less than 40 min.

In contrast, the 3 groups given dexmedetomidine with or without butorphanol generally showed a pattern of improvement in mean behavior and cooperation scores (Tables 2, 3). Dogs given dexmedetomidine at 125 μg/m² as a stand-alone treatment had the least consistent intra-procedural response and smallest improvement in mean cooperation and behavior scores from baseline. For example, mean cooperation scores in the Dex 125 group declined by 8.6 points at 20 min (*n* = 17 dogs) and 2.7 points at 30 min (*n* = 14), then improved by 18.7 points at 40 min (*n* = 9) and by 38.8 points at 50 min (*n* = 6). At the 50-min interval, each of the 6 dogs in this group showed an improvement from baseline.

Dogs in the Dex 375, Dex 125 + Bu, or Dex 375 + Bu groups showed greater improvements in mean behavior and cooperation scores compared to the Dex 125 group. Behavior scores increasingly improved in a generally linear fashion in the Dex 125, Dex 375, Dex 125 + Bu, and Dex 375 + Bu groups. This dose- and drug-related pattern of improvement in mean behavior scores was observed at the 20-, 30-, and 40-min intervals (Table 3). The trends in mean cooperation scores were less consistently related to either the dexemedetomidine dosage or co-treatment with butorphanol. For example, at the 40-min interval, dogs in the Dex 125 + Bu group (*n* = 6) had a 47.5-point improvement in mean cooperation score *versus* a 26.4-point improvement for dogs in the Dex 375 + Bu group (*n* = 5). In general, the greatest improvements in mean intra-procedural behavior and cooperation scores at the various time points occurred when dexmedetomidine was combined with butorphanol.

The economic analysis determined that manual restraint required the largest number of personnel and the longest contact time for purposes of restraint (Table 2). Mean personnel and contact time required for restraint declined progressively as the dexmedetomidine dosage was increased and when butorphanol was added to the pharmacologic regimen. Dex 125 had a comparatively modest impact on mean personnel and contact time required for restraint, resulting in a mean reduction of 7.8 personnel-min compared to manual restraint (35.64 *versus* 43.44). Mean personnel-min declined more than 3-fold, from 35.64 to 11.06, when dexmedetomidine was used at 375 μg/m² instead of 125 μg/m². Further, less dramatic decreases in personnel-min occurred when butorphanol was added to the protocol. The increased personnel-min required by manual restraint resulted in the highest opportunity cost of any of the restraint protocols used in the study, $47.78, which was more than 7-fold higher than Dex 375 + Bu ($6.66), the most economical option in terms of opportunity cost.

Table 4. Labor, drug, and opportunity cost comparison for different restraint options

Restraint protocol[a]	1. Mean labor cost ($) for restraint @ $0.24/min[b]	2. Mean drug cost ($)	3. Mean opportunity cost ($)	4. Mean total cost ($) (columns 1 + 2 + 3)
Manual	10.43	—	47.78	58.21
Dex 125	8.85	6.04	39.20	54.09
Dex 375	2.65	13.91	12.17	28.73
Dex 125 + Bu	1.99	17.47	9.11	28.57
Dex 375 + Bu	1.45	30.85	6.66	38.96

[a] Dex 125 and Dex 375 — dexmedetomidine in μg/m² given IM at 0 min. Bu — butorphanol at 0.4 mg/kg given IM at 0 min. The mean drug cost includes the cost of atipamezole administered after the procedure to reverse dexmedetomidine.
[b] See Appendix for calculation of per-min labor cost for restraint.

When labor, drug, and opportunity costs are combined (Table 4), manual restraint emerges as the least cost-effective restraint protocol despite the absence of any drug cost. Manual restraint combines the highest mean labor cost for restraint ($10.43) with the highest mean opportunity cost ($47.78), for a total mean cost per procedure of $58.21. The Dex 125 + Bu restraint protocol was the most cost effective, with a mean cost per procedure of $28.57, or $29.64 (50.9%) less than manual restraint, followed closely by the Dex 375 protocol. The mean total cost of the Dex 125 protocol was marginally less than the

Table 5. Mean change from baseline of in intra-procedural cooperation scores of dogs following manual or pharmacologic restraint

	Post-treatment interval (minutes) and mean deviation (minus/plus) from baseline score of 0 as midpoint on a 100-point VAS[b]				
Restraint protocol[a]	20	30	40	50	60
Manual restraint (*n* = 18)	−16.7 (−60/33) *n* = 18	−24.9 (−82/4) *n* = 7	0 (−6/4) *n* = 2	NA *n* = 0	NA *n* = 0
Dex 125 (*n* = 17)	−8.6 (−63/48) *n* = 17	−2.7 (−62/49) *n* = 14	18.7 (−29/57) *n* = 9	38.8 (9/57) *n* = 6	8.0 (−47/58) *n* = 3
Dex 375 (*n* = 17)	8.7 (−45/77) *n* = 17	15.8 (−44/81) *n* = 16	6.2 (−17/31) *n* = 9	−39.0 *n* = 1	NA *n* = 0
Dex 125 + Bu (*n* = 19)	15.8 (−43/76) *n* = 19	14.4 (−47/76) *n* = 19	27.8 (−22/67) *n* = 13	47.5 (9/84) *n* = 6	44.3 (4/85) *n* = 4
Dex 375 + Bu (*n* = 19)	19.5 (−60/57) *n* = 19	19.8 (−54/69) *n* = 19	16.6 (−25/69) *n* = 13	26.4 (−4/67) *n* = 5	17.3 (0/44) *n* = 4

[a] Dex 125 and Dex 375 — dexmedetomidine in μg/m² given IM at 0 min. Bu — butorphanol at 0.4 mg/kg given IM at 0 min.
[b] Visual analog scale (VAS) is from agitated (0) to sedate (100), i.e., higher values indicate more controlled behavior.
NA — not applicable.

mean cost of manual restraint, with lower labor and opportunity costs being offset somewhat by drug cost. The Dex 375 + Bu protocol had the lowest mean labor cost and lowest mean opportunity cost but the highest mean drug cost. When all costs were considered, Dex 375 + Bu occupied a middle ground (mean total cost of $38.96) between the highest (manual restraint) and lowest cost (Dex 125 + Bu) protocols.

Although no complications were observed during the procedures, there was a marked decrease in heart rate in dogs receiving dexmedetomidine. After receiving atipamezole, the animals were left undisturbed in a cage in the anesthesia room. This allowed for continuing observation of the animals by the anesthesia personnel while they were completing other tasks. Recovery was uneventful and all dogs receiving atipamezole fully recovered approximately 3 min after administration of the reversal without signs of excitement or any other side effects.

Discussion

This study evaluated dexmedetomidine at its approved canine preanesthetic IM dosages of 125 and 375 μg/m². Dexmedetomidine is also approved at 375 μg/m² IV or 500 μg/m² IM dosage for stand-alone sedation and analgesia in dogs. Whether 500 μg/m² IM dexmedetomidine alone or in combination with butorphanol would produce more profound sedation compared to a lower dose is speculative. Granholm et al (19) found that the 500 μg/m² IM dose given alone provided a similar level of sedation as the 375 μg/m², but had a longer effect. Because dexmedetomidine has a dose-dependent effect, it is possible that 500 μg/m² given as a single-agent treatment may produce further improvements in tractability and intra-procedural behavior outcomes than what was observed in this study, especially for procedures of longer duration (1).

When dexmedetomidine was combined with butorphanol, an additive effect was observed. For example, Dex 125 + Bu and Dex 375 + Bu had a more pronounced effect on behavior scores than Dex 125 or Dex 375, respectively. This result was consistent with earlier studies which demonstrated that medetomidine, the dexmedetomedine precursor, also has a reliable additive effect in dogs when combined with butorphanol (5,8,23).

Mean behavior and cooperation scores improved as the dexmedetomidine dosage increased and when dexmedetomidine was combined with butorphanol. Although this trend was generally true at all time points, the behavior and cooperation responses of individual dogs varied considerably (Tables 3, 5). For example, dogs in the Dex 375 + Bu group had cooperation scores that varied from baseline by minus 60 to plus 57 at the 20-min time point (Table 5). Even dogs controlled by manual restraint showed considerable variation from baseline in behavior and cooperation scores at the 20-minute interval, from minus 60 to plus 33. The decline in behavior and cooperation scores may be due to preexisting arousal and high levels of endogenous catecholamines in some patients prior to sedation or due to manipulation of the patient during the procedure itself. The implication for practitioners is that response to sedation can be variable depending on the individual patient's temperament, physiology, and pre-existing condition. For example, in a prior study a multi-modal anesthesia protocol consisting of 3 agents including dexmedetomidine produced a rapid and profound response in most dogs but only moderate sedation or a light plane of anesthesia in a small minority (5). In other words, a uniform onset, depth, or duration of sedation, or an adequate response in 100% of animals should not be expected, regardless of the sedative dose or protocol used.

Manual restraint is reasonable for cases when the animal's temperament allows, where the procedure is of short duration and non-painful, or where immediate intervention is required. However, manual restraint incurs several well-known risks, including injuries to patients or their handlers, increased stress response in patients, and potential for suboptimal procedural outcome. In fact, manual restraint was the least satisfactory approach compared to any of the pharmacologic regimens evaluated in this study, requiring the largest average number of personnel for restraint (2.4 persons) and the longest average contact time (> 18 min). Dexmedetomidine given as a single agent at the low dose required an average number of restraint personnel and contact time that were nearly as high, 2.2 persons and 16.2 min, respectively. However, when dexmedetomidine was given at 375 μg/m² alone or in combination

with butorphanol, the mean number of personnel required for restraint declined by 42% and 54% and the mean contact time by 56% and 70%, respectively compared to manual restraint (Table 2). In many cases, no additional personnel were required for restraint when dexmedetomidine was given at the high dosage or with butorphanol (Table 2). These results suggest that Dex 375, Dex 125 + Bu, or Dex 375 + Bu can provide adequate sedation for minimally invasive procedures lasting less than 60 min. The favorable behavioral and cooperation scores at the 50- and 60-min time points for Dex 125 + Bu and Dex 375 + Bu (Tables 2 and 3) were encouraging indicators that these combination regimens were suitable for procedures lasting up to 1 h without redosing these drugs.

A conservative economic comparison of the 5 groups would consider only the cost of restraint-associated labor at $0.24/min plus drug cost (columns 1 and 2 in Table 5). From that standpoint, all of the pharmacologic restraint protocols would be less cost-effective than manual restraint, with Dex 125 being the least costly, i.e., $14.89 for restraint-associated labor and drugs *versus* $10.43 for manual restraint. However, in a well-managed practice operating at or near full capacity, the opportunity cost model (see Appendix and Table 4, column 3) is a more accurate measure of the true economic burden borne by the provider of the service. Opportunity cost assumes that every resource can be put to an alternative use. The value of the forgone alternative is the cost of a lost opportunity. Personnel diverted to manual restraint could be utilized for other revenue-generating purposes, representing an opportunity cost. The cost of labor for a non-veterinarian staff member is less than 1/4 that of an individual's revenue-generating capacity ($0.24 *versus* $1.10, see Appendix). Opportunity cost is the most significant of the 3 components of the various restraint protocols (labor, drugs, and lost opportunity). When opportunity cost is considered, any of the pharmacologic protocols is superior to manual restraint, with Dex 125 + Bu being the most cost-effective, followed closely by Dex 375 (Table 4, column 4). This calculation does not consider the intangible but favorable impact that pharmacological restraint may have on procedural quality, a more positive experience for the patient, and the client's perception of the practitioner's technical skills and humanitarian approach to treatment. Nor does it take into account the possible negative effect that resistance to manual restraint might have on the patient's attitude during future visits.

To the authors' knowledge, this is the first published report evaluating the economic and human resource impact of parenterally administered alpha-2 agonist sedation in companion animal medicine. However, an extensive body of evidence-based research has affirmed the clinical and economic benefits of dexmedetomidine in human medicine, primarily due to greater patient tractability, lower procedural cost, shorter hospitalization stays, and lower drug cost compared to alternative drug therapies (24,25). For example, recent US and Canadian randomized clinical trials comparing intensive care unit (ICU) patients who received extended sedation with dexmedetomidine or injectable midazolam determined that dexmedetomidine patients had significantly lower total hospitalization costs (26,27). This was primarily due to shorter ICU stays and significantly lower need for ventilator-assisted respiration, an intervention associated with increased morbidity, mortality, and excess cost. Implicit in avoiding rescue therapy such as mechanical ventilation is lower opportunity cost.

Limitations of the study were the small number of dogs (n = 90) and random allocation of dogs to treatment groups in the sequence in which they were enrolled rather than by type of procedure and different procedure lengths. Criteria such as procedure length or difficulty would impact dogs undergoing manual restraint more than those given pharmacological sedation. Since the study was not powered based on procedural criteria, a valid statistical analysis that compares behavior and cooperation results was not possible. Additionally, the nature of the study, and the fact that the handlers were probably able to deduce which dogs received pharmacologic restraint and which dogs did not, may have introduced bias as to how the dogs were handled or assessed.

The preliminary study reported here nevertheless suggests that pharmacologic restraint contributes to more favorable intraprocedural patient behaviors and cooperation and a superior economic return to the practice. Based on the results of this study, sedation with dexmedetomidine at 125 and 375 $\mu g/m^2$ with butorphanol at 0.4 mg/kg IM for non-invasive and minimally invasive procedures in healthy dogs can be recommended over manual restraint.

Acknowledgments

The authors acknowledge the contribution of Mark Dana of Scientific Communications Services, LLC in the writing and editing of the manuscript, and of Deborah Amodie of Zoetis Inc for providing statistical review and analysis. We are grateful to personnel at the University of Minnesota Veterinary Medical Center who provided clinical care and data collection support for the study and to Zoetis Inc who provided the drugs for the study and funding to pay technical personnel involved in data collection.

CVJ

Appendix. Economic assumptions used to calculate opportunity cost and cost of labor used for restraint

Average value	Economic factor
Calculation of opportunity cost	
1. $132 416[a]	Annual revenue generated per non-veterinarian FTE[b] working 2000 h/year
2. $66.21	Hourly revenue generated by non-veterinarian FTE (item 1 ÷ 2000 h)
3. $1.10	Revenue per minute generated by non-veterinarian FTE (item 2 ÷ 60 min) = opportunity cost (used in Tables 1 and 5)
Calculation of labor cost for restraint	
4. $29 710[c]	Annual salary for animal health technician
5. $14.85	Hourly salary for animal health technician (item 4 ÷ 2000 h)
6. $0.24	Per-minute salary for animal health technician (item 5 ÷ 60) = labor cost for restraint (used in Table 4)

[a] American Animal Hospital Association, Financial & Productivity Pulse Points. 7th ed. 2013.
[b] FTE — full-time equivalent.
[c] Bureau of Labor Statistics, US Department of Labor. US Occupational Outlook Handbook, 2012–2013 ed. Available from: http://www.bls.gov/ooh/healthcare/veterinary-technologists-and-technicians.htm Last accessed January 11, 2016.

References

1. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: A novel sedative-analgesic agent. Proc Bayl Univ Med Cent 2001;14: 13–21.
2. Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an alpha 2-adrenoceptor agonist. Eur J Pharmacol 1988;150:9–14.
3. Dexdomitor Freedom of Information Summary. Orion Corporation. NADA 2006:141–267.
4. Kuusela E, Raekallio M, Anttila M, Falck I, Mölsä S, Vainio O. Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. J Vet Pharmacol Ther 2000;23:15–20.
5. Barletta M, Austin BR, Ko JC, Payton ME, Weil AB, Inoue T. Evaluation of dexmedetomidine and ketamine in combination with opioids as injectable anesthesia for castration in dogs. J Am Vet Med Assoc 2011;238:1159–1167.
6. Girard NM, Leece EA, Cardwell J, Adams VJ, Brearley JC. The sedative effects of low-dose medetomidine and butorphanol alone and in combination intravenously in dogs. Vet Anaesth Analg 2010;37:1–6.
7. Ko JC, Barletta M, Sen I, et al. Influence of ketamine on the cardiopulmonary effects of intramuscular administration of dexmedetomidine-buprenorphine with subsequent reversal with atipamezole in dogs. J Am Vet Med Assoc 2013;242:339–345.
8. Kuo WC, Keegan RD. Comparative cardiovascular, analgesic, and sedative effects of medetomidine, medetomidine-hydromorphone, and medetomidine-butorphanol in dogs. Am J Vet Res 2004;65:931–937.
9. Mendes GM, Selmi AL, Barbudo-Selmi GR, Barbudo-Selmi GR, Lins BT, Figueiredo JP. Clinical use of dexmedetomidine as premedicant in cats undergoing propofol-sevoflurane anaesthesia. J Feline Med Surg 2003;5:265–270.
10. Selmi AL, Mendes GM, Lins BT, Figueiredo JP, Barbudo-Selmi GR. Evaluation of the sedative and cardiorespiratory effects of dexmedetomidine, dexmedetomidine-butorphanol, and dexmedetomidine-ketamine in cats. J Am Vet Med Assoc 2003;222:37–41.
11. Vickery RG, Sheridan BC, Segal IS, Maze M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an alpha 2-adrenergic agonist, in halothane-anesthetized dogs. Anesth Analg 1988;67:611–615.
12. Sinclair MD. A review of the physiological effects of alpha 2-agonists related to the clinical use of medetomidine in small animal practice. Can Vet J 2003;44:885–897.
13. MacDonald E, Scheinin M, Scheinin H, Virtanen R. Comparison of the behavioral and neurochemical effects of the two optical enantiomers of medetomidine, a selective alpha-2-adrenoceptor agonist. J Pharmacol Exp Ther 1991;259:848–854.
14. Savola JM, Virtanen R. Central alpha 2-adrenoceptors are highly stereoselective for dexmedetomidine, the dextro enantiomer of medetomidine. Eur J Pharmacol 1991;195:193–199.
15. Kuusela E, Raekallio M, Väisänen M, Mykkänen K, Ropponen H, Vainio O. Comparison of medetomidine and dexmedetomidine as premedicants in dogs undergoing propofol-isoflurane anesthesia. Am J Vet Res 2001;62:1073–1080.
16. Ansah OB, Raekallio M, Vainio O. Comparison of three doses of dexmedetomidine with medetomidine in cats following intramuscular administration. J Vet Pharmacol Therap 1998;21:380–387.
17. Kuusela E, Raekallio M, Hietanen H, Huttula J, Vainio O. 24-hour Holter-monitoring in the perianaesthetic period in dogs premedicated with dexmedetomidine. Vet J 2002;164:235–239.
18. Murrell JC, Hellebrekers LJ. Medetomidine and dexmedetomidine: A review of cardiovascular effects and antinociceptive properties in the dog. Vet Anesth Analg 2005;32:117–127.
19. Granholm M, McKusick BC, Westerholm FC, Aspegren JC. Evaluation of the clinical efficacy and safety of intramuscular and intravenous doses of dexmedetomidine and medetomidine in dogs and their reversal with atipamezole. Vet Rec 2007;160:891–897.
20. Leppänen MK, McKusick BC, Granholm MM, Westerholm FC, Tulamo R, Short CE. Clinical efficacy and safety of dexmedetomidine and buprenorphine, butorphanol or diazepam for canine hip radiography. J Small Anim Pract 2006;47:663–669.
21. Eckermann S, Pekarsky B. Can the real opportunity cost stand up: Displaced services, the straw man outside the room. Pharmacoeconomics 2014;DOI 10.1007/s40273-014-0140-3.
22. Posnett J, Jan S. Indirect cost in economic evaluation: The opportunity cost of unpaid inputs. Health Econ 1996;5:13–23.
23. Hayashi K, Nishimura R, Yamaki A, et al. Comparison of sedative effects induced by medetomidine, medetomidine-midazolam and medetomidine-butorphanol in dogs. J Vet Med Sci 1994;56:951–956.
24. Canadian Agency for Drugs and Technologies in Health. Dexmedetomidine for sedation of patients in the ICU or PICU: Review of Cost effectiveness and guidelines. CADTH Rapid Response Reports. 2014.
25. Hoy SM, Keathing GM. Dexmedetomidine: A review of its use for sedation in mechanically ventilated patients in an intensive care setting and for procedural sedation. Drugs 2011;71:1481–1501.
26. Dasta JF, Kane-Gill SL, Pencina M, et al. A cost-minimization analysis of dexmedetomidine compared with midazolam for long-term sedation in the intensive care unit. Crit Care Med 2010;38:497–503.
27. Lachaine J, Beauchemin C. Economic evaluation of dexmedetomidine relative to midazolam for sedation in the intensive care unit. Can J Hosp Pharm 2012;65:102–110.