TITLE: Effect of Insulin and Fasting Regimen on Blood Glucose Concentrations of Diabetic Dogs during Phacoemulsification

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RETROSPECTIVE STUDY

Effect of Insulin and Fasting Regimen on Blood Glucose Concentrations of Diabetic Dogs during Phacoemulsification

Abstract

This study aimed to compare four protocols for preanesthetic insulin administration and fasting time with respect to the variation of intraoperative blood glucose (BG) concentrations versus preanesthetic values (baseline). The patient records of dogs undergoing cataract surgery were included. Data on anesthetic protocols, comorbidities, and intraoperative complications (hyper- and hypoglycemia, hypotension, hypothermia, and bradycardia) were analyzed. The insulin/fasting protocols included (A) 12 hr fasting and half insulin dose, (B) 6 hr fasting and half insulin dose, (C) 12 hr fasting and full insulin dose, and (D) 12 hr fasting and no insulin. Forty-eight dogs were included (14 in A, 10 in B, 13 in C, and 11 in D). Protocol D resulted in a significant increase of intraoperative BG concentrations compared with baseline ($P = .001$), whereas in the remaining groups, the baseline BG did not differ from intraoperative values. There were no statistically significant associations between the treatment group and the occurrence of intraoperative complications or the presence of diagnosed comorbidities. In conclusion, different insulin and fasting regimen protocols may be used for diabetic patients with no apparent benefit or risk from one protocol versus another. The use of insulin before surgery results in lesser increase of BG intraoperatively as compared with preanesthetic values. However, whether this should be interpreted as better perioperative control of glycemia remains debatable.

Abbreviations

BG (Blood glucose); (BCS) Body Condition Score

Introduction

Diabetes mellitus is a systemic disease whose prevalence in the canine population in the UK has been reported as 0.32%.[1] Diabetic cataract is one of the most common complications of this endocrine disorder in dogs and can be treated surgically.[2]

Diabetes mellitus poses some anesthetic challenges owing to the possible co-morbidities such as kidney dysfunction, hyperadrenocorticism, systemic hypertension and peripheral neuropathies.[3] In addition, chronic hyperglycemia with BG concentrations higher than the renal threshold (12-14 mmol/L) results in osmotic diuresis, dehydration and electrolyte imbalances such as hyponatremia, hypokalemia and hypophosphatemia. [3]

Changes in basal metabolism and body temperature, the stress response, the requirement for fasting and a disruption of the normal exercise routine, all of which ordinarily accompany anesthesia, have the potential to perturb the glycemic control of well medically controlled diabetic dogs. As a result, in diabetic patients, the risk of poor glucose regulation is likely to be increased in the perioperative period, which may exacerbate the deleterious effects of hyperglycemia on the body homeostasis. Besides hyperglycemia, diabetic dogs undergoing surgery may experience hypoglycemia as a result of a combination of administration of insulin and preanesthetic fasting.

Although the perturbation of glucose homeostasis in diabetic patients is of concern among clinicians, the most effective insulin/fasting protocol in terms of optimal intra-operative control of blood glucose (BG) concentrations has not been identified yet, and clear guidelines are lacking. Some authors have recommended SC administration of either a full or a fractional dose of insulin on the morning of the surgery after 12 hours of fasting.[4,5] However, the effectiveness of these protocols has never been evaluated. A more recent study compared a quarter of a dose of insulin versus a full dose administered before anesthesia in dogs fasted for 12 hours, and found that the full dose offered only marginal advantages over the quarter-dose, as poorly controlled hyperglycemia developed in both cases.[6] Some textbooks aimed at general practitioners provide guidelines on how to handle insulin and food for diabetic dogs the morning of surgery, but there is no general consensus between authors regarding the dose of insulin or the administration or withholding of food.[3,7,8] As a result, the choice of the insulin/fasting protocol is based on the subjective preference of the clinician.

The primary aim of this retrospective study was to compare 4 protocols for insulin dose and fasting time with respect to the variation of intra-operative BG concentrations versus pre-anesthetic values (baseline), in diabetic dogs undergoing cataract surgery. A secondary aim was to determine whether there was an association between the choice of the insulin /fasting regimen and the occurrence of perianesthetic complications, namely hypothermia, hypotension, hyper- and hypoglycemia, and bradycardia. A further secondary objective was to investigate whether the choice of the anesthetic protocol could produce an effect on the intra-operative BG concentrations.

The authors hypothesized that preoperative administration of insulin would maintain better glucose control and be associated with fewer intraoperative complications than withholding of insulin on the day of surgery in diabetic dogs. It was also hypothesized that poorly controlled intra-operative hyperglycemia would increase the risk for intra-operative complications.

Materials and Methods

Case selection criteria and medical records review

The study was conducted under approval of the Clinical Research Ethical Review Board of the Royal Veterinary College (license number: 2017-1017).

The medical records of all the dogs with diagnosed diabetes mellitus undergoing elective phacoemulsification at the Queen Mother Hospital for Animals (QMHA) of the

Royal Veterinary College between October 2012 and October 2017 were reviewed. The cases were identified through the database, by using the following key word-combinations: "dog/canine + diabetic/diabetes + anesthesia/anesthetic", "dog/canine + insulin + anesthesia/anesthetic", "dog/canine + cataract surgery", and "dog/canine + phacoemulsification". Additionally, a list of the canine patients undergoing phacoemulsification was obtained through the internal logbook for surgical procedures. The search was manually refined and the incomplete patient files, as well as the records of non-diabetic dogs undergoing phacoemulsification, were excluded. Demographic data of the patients enrolled in the study (sex, age, breed and Body Condition Score (BCS)) were also collected and used for statistical analysis. Fructosamine serum concentrations, as well as the presence of co-morbidities, were noted when this information was available on the record. The last BG concentration measured in each patient before anesthesia was recorded as the pre-anesthetic BG value (baseline). The information on whether insulin and/or glucose were administered during the anaesthetic was also recorded.

Definitions and treatment groups

The following events occurring during anesthesia were considered peri-anesthetic complications and defined as follows:

- Hyperglycemia (BG >250 mg/dL or 13.9 mmol/L);[6]
- Hypoglycemia (BG <70 mg/dL or 3.9 mmol/L);[6]
- Hypothermia (rectal body temperature <36.7 Celsius);[9]
- Hypotension (either mean arterial pressure <54 mmHg measured with oscillometry, or as systolic arterial pressure <90 mmHg measured with Doppler);[10] and
- Bradycardia (heart rate <60 beats per minute in the presence of hypotension as above defined).[11]

Clinician-dependent peri-operative insulin/fasting time regimen protocols used at our institution led to the identification of the following treatment groups:

- Group A: half of the usual insulin dose administered SC on the morning of surgery in dogs fasted for 12 hours;
- Group B: half of the usual insulin dose administered SC on the morning of surgery in dogs fasted for 6 hours;
- Group C: the dog's full insulin dose administered SC on the morning of surgery after 12 hours fasting; and
- Group D: fasting time set at 12 hours and no pre-operative insulin; intra-operative insulin to be administered at the anesthesist's discretion based on the BG concentrations measured during the anesthetic.

In order to investigate whether the choice of the anesthetic protocol could produce an effect on the intra-operative BG concentrations, all data were pulled together again using the anaesthetic protocol as a grouping factor. The following two possible treatment groups were identified, based on the most common anesthetists' choices at the QMHA:

- Group AO (Acepromazine-Opioid): acepromazine[a] and an opioid - either methadone[b] or pethidine[c] or butorphanol[d] in premedication; and
- Group O (Opioid): opioid-based premedication (either methadone or pethidine or butorphanol).

Whether animals received one or another premedication, they were induced with propofol[e] or alfaxalone[f] followed by inhalational anesthesia with either sevoflurane[g] or isoflurane[h] delivered in oxygen.

Data analysis

Descriptive statistics applied for demographic data. Normality of data was assessed with the Kolmogorov-Smirnov test. . Either one-way repeated measures analysis of variance or Friedman repeated measures analysis of variance on ranks were used, depending on data distribution, to evaluate changes in intraoperative BG concentrations within each treatment group, whereas the groups were compared with respect to the intraoperative BG concentrations with Kruskal-Wallis one-way analysis of variance on ranks. Item imputation was applied to substitute missing values.[12] Two-way analysis of variance, with time and treatment (AO and O) as source of variation factors, was used to evaluate the effect of the anesthetic protocol on the BG concentrations over time. The proportions of dogs experiencing intra-operative complications, as well as of those receiving intraoperative insulin, within each set of treatment groups (A, B, C and D; AO and O) were analysed with $\chi 2$ and Fisher exact tests, respectively. For groups A–D comparisons, if an overall difference was detected between groups with respect to one of the aforementioned variables (intraoperative complications and intraoperative insulin administration), then the $\chi 2$ test was followed by an additional Fisher exact tests for pairwise comparison.

Commercially available software[i,j,k] were used. *P* values lower than 0.05 were considered statistically significant.

Results

Data are presented as either means and standard deviation, or medians and interquartile (25 and 75%) ranges, where it applies.

The initial search identified 114 files that were then revised and screened. A total of 48 dogs of various breeds, consisting of 31 (all of whom were castrated) and 17 females (15 of whom were spayed), all on treatment with an intermediate-acting insulin product[l] at the time of surgery, met the inclusion criteria and were included in the study. The 48 dogs still included after screening were operated between January 2013 and December 2017. Dogs were prescribed a drop of dexamethasone phosphate 0.1%[m] to be applied topically onto the affected eye/s once every other day, or once daily, for as many days as the patient had to wait before the surgery, which was routinely between 2 to 14 days, depending on the surgery schedule. Immediately postoperatively, the same drops were continued for life. No other pre-operative ocular medical treatment was regularly given with the exception of tropicamide[n] to dilate the pupil and topical flurbiprofen[o], both given alternatively every 15 minutes for 1 hour, 1 to 2 hours immediately before induction, in preparation for the pre-operative electroretinogram that was performed in all the patients. In the majority of the patients, the baseline BG concentrations were above the reference ranges provided for dogs by the laboratory of our institution (3.6–7.0 mg/dL), namely, 22 (19–30), 17 (12–22), 16 (15–26), and 17 (9–21) mg/dL in groups A, B, C, and D, respectively. The difference in baseline BG between groups was not statistically significant (P = .19). The proportion of nonhyperglycemic dogs (including both the hypoglycemic and the normoglycemic ones, based on the preanesthetic BG measurement) was lower in groups A (0%; n = 0) and B (9%; n = 1 normoglycemic dog) than in the remaining groups C (30%; n = 3 normoglycemic dogs) and D (36%; n = 1 hypoglycemic dog and 3 normoglycemic dogs).[6] This difference was statistically significant (*P* = .013). IV atracuriump was administered intraoperatively to all patients (dose range: .1–.3 mg/kg). The neuromuscular block was monitored through a nerve stimulator with a train-of-four stimulating pattern, and reversed with intramuscular neostigmine[q] (dose range: .01–.03 mg/kg) and glycopyrroniumr (dose range: .01–.02 mg/kg) at the end of surgery, if the train-of-four ratio was <.9.[13] Intermittent positive-pressure ventilation was provided to all dogs during the neuromuscular block.

Data pertaining age (119±24 months) and fructosamines serum concentrations (502 ± 234 µmol/L; n = 12) showed normal distribution, whereas total BG concentration (including preanesthetic and intraoperative values in all groups; 19 [12–27] mg/dL) was not normally distributed. Six out of the 12 measured fructosamines serum concentrations were >500 µmol/L. Body condition score (5 [4–5]/9) was recorded in 34 out of 48 files only. Pre- and intraoperatively, the glycemia was assessed on whole blood with a glucometer specifically designed for veterinary patientss. The time interval between subsequent intraoperative BG concentrations measurements was 30 min. At least one missing intraoperative BG value was found in 25% (n = 12) of the files. Therefore, a total of 19 out of 240 BG concentrations were replacement values obtained with data imputing.

Intra-operative BG concentrations changed significantly compared to baseline values only in group D (*P*=.014; **Figure 1**). Overall, the four treatment groups (with insulin/fasting regime as treatment factor) were compared with respect to intraoperative BG concentrations, a statistically significant difference was found only between group B (14 [10–22] mg/dL) and group D (30 [17–34] mg/dL; $P = .005$).

Regarding the choice of the anesthetic protocol, 42% of the dogs (n = 20) were included in group AO, whereas group O was composed of the remaining 58% (n = 28). The BG concentrations over time were not affected by the choice of the anesthetic protocol (P = .36). In group D, the frequency of intraoperative administration of insulin, carried out on a case-by-case basis at the anesthetist's discretion, was higher than in any other group, and this difference was statistically significant ($P < .001$; **Table 1**). None of the patients experienced intraoperative hypoglycemia. There were no statistically significant associations between the treatment group (A, B, C, or D; AO or O) and the occurrence of intraoperative complications or the presence of underlying diagnosed comorbidities. The comorbidities represented in the study population were mitral valve disease (n = 7), chronic bronchitis (n = 1), pancreatitis (n = 6), gall bladder mucocele (n = 1), and hyperadrenocorticism (n = 5). Of the 16 patients with diagnosed comorbidities, 25% (n = 4) had more than one condition at the same time. The proportions and numbers of dogs experiencing intra-operative complications within each treatment group are shown in Table 1.

Discussion

The findings of this study indicate that the use of insulin before surgery results in lesser increase of BG intraoperatively, as compared with preanesthetic values, than insulin withdrawal.

Anesthesia may alter the delicate endocrine balance of diabetic patients by triggering a stress response through a complex interplay involving the hypothalamic–pituitary axis, the neuroendocrinal system, and the autonomic nervous system.[14] The net result of such neuro-endocrinal outflow is a hypermetabolic state characterized by hyperglycemia.[14] Unsurprisingly increases in cortisol and BG concentrations are commonly observed during anesthesia in non-diabetic animals and humans.[14-16] Presumably, patients with diabetes mellitus, especially if the condition is poorly controlled medically, may experience a less predictable, and possibly more pronounced, neuro-endocrine response to anesthesia, resulting in uncontrolled hyperglycemia. If this were true, it would be reasonable to expect the hyperglycemia to be at least partially refractory to the usual insulin dose, and more challenging to stabilize in case of pre-operative insulin withdrawal.

The preoperative administration of half insulin dose is a common choice at the referral center where the study was carried out. In dogs fasted for 6 hr, the rationale behind this protocol is the need to control the perioperative glycemia in diabetic patients whose surgery is scheduled in the early afternoon. These patients are fed a light meal (usually half of their canned food dose) ~6 hr before surgery, and the clinicians halve the insulin dose in an attempt to avoid sudden hypoglycemia because the food intake is smaller than usual. At our referral center, some anesthetists also halve the insulin after 12 hr of fasting in order to reduce the chances of a dog developing a hypoglycemic episode after having received insulin and no food.

Altogether, these findings suggest that administering insulin in the pre-anesthetic period may be a better clinical choice than not administering it. This information may be of help when making general recommendations and supporting the development of future studies. However, it is worth to mention that stability of the BG concentrations throughout the peri-operative period does not necessarily imply an adequate medical control of diabetes, a condition whose clinical evaluation is complex and should be based on more than one parameter. Moreover, clinicians need to be aware that pre-operative fasting requires frequent checking of a patient's BG concentrations to prevent a hypoglycemic episode.

Although the baseline BG concentrations obtained prior to anesthesia were not statistically different between groups, it is worth considering that nonhyperglycemic dogs were more represented in group D than in the other groups. This could have affected the decision of the anesthetists in charge not to administer preoperative insulin, as reasonably the clinicians would have been more likely to withhold insulin in hypoglycemic and normoglycemic patients rather than in dogs with hyperglycemia.

As it is generally advised that patients should be in as optimal a general health condition as possible for general anesthesia, one could assume that most patients referred for an elective procedure have achieved adequate stabilization of any underlying medical condition prior to the referral for anesthesia and surgery. Unfortunately, this is not always the case. Although fructosamine serum measurements were available only in a few patients, it should be noted that half of the values were above 500 µmol/L, which has been defined as the cut off value for a poorly controlled condition.[17] It is possible that patients without fructosamine readings had sub-optimal glycemic control. If this were true, it would be reasonable to assume that poorly controlled diabetes, a condition that might exacerbate the effect of anesthesia on the glycemic control, could have been common in the study population. It should be recommended as standard practice that diabetic patients for whom general anesthesia is scheduled undergo not only routine preanesthetic baseline BG measurement but also a thorough medical evaluation of the diabetes, which might include fructosamine assay or glycemic curves, before being anesthetized.

As a result of its retrospective nature, this study has several limitations. Some of the patients who had been included in the study after a preliminary search had incomplete files for which they had to be excluded, or had their last preanesthetic BG concentration measured days or even weeks before the day of surgery, a drawback that, owing to the day-to-day variability of BG in diabetic dogs, could have jeopardized the accuracy of our findings.18 This reduced considerably the number of patients to be included in the study, which may potentially represent a further source of bias. Another limitation pertains to the intraoperative BG concentrations, which were measured at ~30 min intervals in most patients but not all as a result of financial constraints, or at the anesthetist's discretion in cases with good glycemic control, where more frequent measurements were not deemed to be necessary. The data could be analyzed despite the missing values by applying item imputation, a statistical procedure widely used for this purpose.[12] Further limitations worth consideration are the possible effect of the topical steroid, administered in the preoperative period and possibly absorbed systemically, on the glucose homeostasis,[19] and the different sizes of the treatment groups, which is suboptimal. Finally, using patients undergoing cataract surgery helped focus the case capture effort and created a standardization of the cohort, but it risks adding a selection bias.

Future studies should be prospective and standardize the time at which the baseline BG measurements are taken, randomize treatment groups that ideally would be of equal sizes and including as many diabetic patients as possible to avoid a potential selection bias based on the presence of ophthalmic problems.

Conclusion

Several different insulin and fasting protocols may be used to anesthetize diabetic patients, with no clear benefit or risks from one protocol versus another. Compared with administration of either full or half insulin dose after 12 hr of fasting, or of half the insulin dose after 6 hr of fasting, administering no insulin on the morning of anesthesia in diabetic dogs resulted in greater increases of intraoperative BG, compared with preanesthetic values. Clinicians in charge of anesthetizing normoglycemic dogs were likely prompted to withhold the insulin on the morning of surgery; however, there is no evidence that this decision resulted in long-term differences in patient outcomes. These findings provide a basis for future prospective studies in diabetic dogs of insulin/fasting protocols prior to anesthesia.

FOOTNOTES

[a] Acecare; Animalcare, UK

[b] Methadone Hydrochloride; Martindale Pharmaceuticals, UK, or Synthadon; Animalcare, UK

[c] Pethidine injection; Martindale Pharmaceuticals, UK

[d] Alvegesic; Dechra, Italy

[e] Propofol-® Lipuro; Virbac, Italy

[f] Alfaxan; Jurox, UK

[g] Sevoflo; Abbott, USA

[h] Isoflo; Abbott, USA

[i] SPSS Statistics 23; IBM Inc., Chicago, IL, USA

[j] NCSS 9 and Pass 12 Statistical Software, NCSS LLC, NV, USA

[k] SigmaStat 4.0 and SigmaPlot 14; Systat Software Inc, CA, USA

[l] Caninsulin; Intervet, UK

[m] Maxidex (R); Novartis Pharmaceuticals, Camberley, UK

[n] Minims (R), Bausch and Lomb, Kingston upon Thames, UK

[o] Ocufen (R); Allergen, Marlow, UK

[p] Tracrium; GlaxoSmithKline, UK

[q] Neostigmine Methylsulfate injection; Hameln Pharmaceutical, UK

[r] Glycopyrronium Bromide; Martindale Pharmaceutical, UK

[s] Alphatrak2; Abbott Laboratories, Abbott Park, IL, USA

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Figure legends

FIGURE 1 Effects of four different insulin/fasting regimens (groups A, B, C, and D) on the intraoperative blood glucose concentrations over time (1: baseline; 2: 30 min; 3: 60 min; 4: 90 min; 5: 120 min after anesthetic induction). The upper and lower quartiles (interquartile range box) represent the data greater (25%) and lesser (25%) than the median, respectively, accounting for 50% of the total data. The whiskers represent the ranges for the bottom 25% and the top 25% of the data values. The dots represent the outliers. The stars indicate statistically significant differences (P = .001) compared with baseline values.

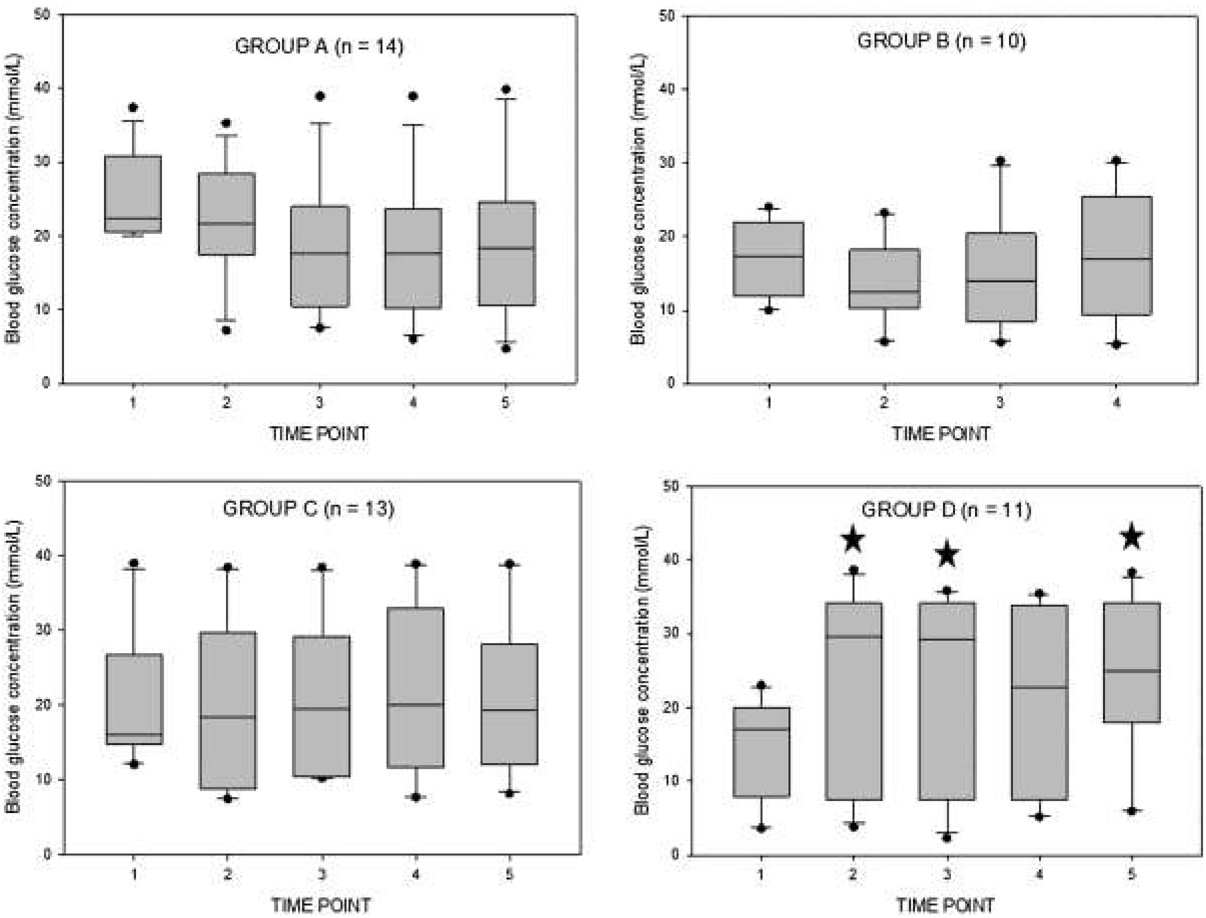

TABLE 1

Proportions and numbers of dogs, within each treatment group, experiencing intra-operative complications (hypotension, bradycardia and hyperglycemia), requiring intra-operative (IO) insulin administration and with a clinical history of co-morbidities.

Group	Hypotension	Bradycardia	Hyperglycemia	Hypothermia	Co-morbidities	IO insulin
A	45% (n=9) *P*= .43	10% (n=2) *P*= .17	80% (n=16) *P*= .36	50% (n=10) *P*= .63	50% (n=10) *P*= .32	20% (n=4) *P*= .13
B	50% (n=6) *P*= .43	8% (n=1) *P*= .17	83% (n=10) *P*= .36	33% (n=4) *P*= .63	42% (n=5) *P*= .32	25% (n=3) *P*= .13
C	72% (n=16) *P*= .43	0% (n=0) *P*= .17	82% (n=22) *P*= .36	41% (n=9) *P*= .63	23% (n=5) *P*= .32	18% (n=4) *P*= .13
D	50% (n=6) *P*= .43	17% (n=2) *P*= .17	50% (n=6) *P*= .36	33% (n=4) *P*= .63	17% (n=3) *P*= .32	42% (n=5) *P*= .13
AO	52% (n=15) *P*= .62	7% (n=2) *P*= .33	90% (n=26) *P*= .23	55% (n=16) *P*= .62	21% (n=6) ***P*= .04**[*]	24% (n=7) *P*= 1
O	55% (n=20) *P*= .62	8% (n=3) *P*= .33	62% (n=23) *P*= .23	40% (n=15) *P*= .62	46% (n=17) ***P*= .04**[*]	24% (n=9) *P*=1

[*] statistically significant