A THESIS FOR THE DEGREE OF MASTER

Retrospective Study of Switching to Insulin Glargine from Neutral Protamine Hagedorn Insulin in Canine Diabetes Mellitus

개 당뇨병 환자에서 인슐린 NPH로부터 인슐린 Glargine 으로의 전환 효과 연구

2016년 2월

서울대학교 대학원

수의과대학 수의내과학 전공

이 지 예

Abstract

Retrospective Study of Switching to Insulin Glargine from Neutral Protamine Hagedorn Insulin in Canine Diabetes Mellitus

이 지 예 (JIYE LEE)

Supervised by Prof. Hwa-Young Youn

수의내과학 (Department of Veterinary Internal Medicine)

The Graduate School of Veterinary Medicine

Seoul National University

This is the retrospective study investigated the glycemic control effect of insulin glargine in canine Diabetes. 32 dogs were included which were treated at Seoul National University Veterinary Medical Teaching Hospital (SNU VMTH) from 2009 January to 2014 January. 17 dogs were treated with NPH (Neutral Protamine Hagedorn) insulin before. They have needed to switch from NPH-based regimen to a glargine-based regimen, due to poor glycemic control by NPH. In the other hand, 15 dogs were treated with NPH insulin and well glycemic controlled.

In each group, patients were analyzed for physical examination, CBC, serum biochemical profile, abdominal imaging, their glucose curve including time to duration, blood glucose nadir, dose of insulin, body weight. Data was analyzed by paired t-test with SPSS statistics program. Compared to the NPH group, duration time was prolonged to 54% after switching insulin type in glargine group. In both group, body weight gradually increased. Compared to NPH group, serum fructosamine level in glargine group had tendency to decrease with the passage of the time. 20.0% patients in NPH group and 17.6% patients in glargine group had shown ketonuria. Hypoglycemia was observed in 13.3% patients in NPH group while 5.9% patients in glargine group.

These results suggest that it is better to switch into glargine in dogs which have some problems about short duration time, frequent occurrence of ketone in urine and high level in serum fructosamine concentration with NPH insulin.

Key words: glargine, NPH; insulin; Mellitus Diabetes ; dog; fructosamine

Student number: 2014-21946

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1. Introduction

Diabetes mellitus is a common endocrine disease in dogs. The prevalence of diabetes mellitus in dogs varies by region, ranging from 0.34% to 1.33%. Type 1 diabetes (formerly known as insulin-dependent diabetes mellitus) accounts for most canine diabetes mellitus cases. Insulin therapy is important for treatment of canine diabetes mellitus due to deficiency of endogenous insulin. The therapeutic effect of insulin may vary depending on the type, dose, frequency, and injection timing of the drug. Although insulin therapy can relieve clinical symptoms, excessive insulin use can cause hypoglycemia. It is therefore important to select appropriate type and dosage of insulin according to the condition of each patient.

There are various types of insulin, with different characteristics. Commonly used insulin types in dogs and cats include intermediate-acting insulin (lente, NPH) and long-acting basal insulin (insulin glargine, insulin detemir, protamine zinc insulin). NPH insulin is a recombinant human insulin, developed in 1946, that is commonly used in canine diabetes mellitus. Because the mean time to glucose nadir is 4 hours and the duration of action is about 10 hours, it is adjusted twice a day in diabetic dogs.

However, because NPH insulin has a pronounced peak concentration, it may increase the risk of hypoglycemia - a common complication of insulin therapy. Insulin glargine is a long-acting insulin analog, with two arginine residues added to the end of the B chain, and an asparagine to glycine substitution at amino acid 21. These changes render the glargine more soluble at acidic pH. Due to this molecular structural change, insulin glargine has a longer peakless duration of action compared to NPH. NPH insulin is the most commonly used initial insulin therapy. Because insulin glargine is absorbed slowly and has a relatively constant effect, it is commonly used in humans once a day as a basal insulin, with little risk of hypoglycemia.

There have been many clinical studies of insulin glargine in human medicine. These studies offer a variety of information such as dose, frequency, combination with other insulin types, injection time, and even the cost of insulin glargine treatment. However, there are few clinical studies of the use of insulin glargine in naturally occurring canine diabetes. The purpose of the study was to evaluate the utility of insulin glargine for glycemic control in canine diabetes patients that exhibit poor glycemic control on NPH insulin.

2. Material and Methods

2.1. Study design

Medical records of canine diabetic patients treated at the Seoul National University Veterinary Medical Teaching Hospital (SNU-VMTH) from January 2009 to December 2014 were reviewed. Patients were divided into two groups (Figure 1) ; the first included 15 patients that had been treated with NPH insulin for at least 1 year (NPH group), the second included 17 patients that had initially been treated with NPH insulin, but exhibited poor glycemic control after more than 3 months of treatment. Therefore insulin type was changed to insulin glargine (glargine group). If hyperglycemia persisted despite NPH insulin treatment, the insulin type was switched to glargine by decision of the treating physician. The insulin regimen was twice - daily injection in all dogs.

2.2. Data collection

Blood was sampled from the saphenous vein, and blood glucose

concentrations measured by portable glucometer. Canine patients visiting to the SNU-VMTH, were fed their usual diet after measurement of fasting blood glucose levels. Blood glucose concentrations were measured every 1 or 2 hours until duration time was determined. Insulin dose was adjusted by the treating physicians according to glucose curve, clinical signs, body weight change, and patient's condition. All patient data, including duration time, blood glucose value at nadir, fasting glucose concentration, insulin dose, and body weight, were recorded on glucose curves at every visit to SNU-VMTH. Duration time is defined as the time at which the blood glucose value rise to 250 mg/dL after the nadir from fasting.

When they have been diagnosed with diabetes, all data include history, physical examination, complete blood count, serum biochemical profile, electrolytes analysis, abdominal X-ray, abdominal ultrasound, and urinalysis. If the presence of other disease (such as an endocrine disorder) was suspected, all examinations necessary for diagnosis were performed. Patients with concurrent diseases (e.g., bacterial cystitis, hyperadrenocorticism, cystolith, pancreatitis, early stage tumor) had received appropriate treatment for these conditions. Dogs with severe systemic disease (e.g., renal failure, hepatic failure, sepsis) were excluded from the study. Concurrent diseases and food type were recorded.

Hypoglycemia was defined as blood glucose ≤ 60 mg/dL. Symptomatic hypoglycemia was determined on the basis of observations by the patient's owner or the treating physicians at SNU-VMTH.

For the serum fructosamine analysis, only patients with baseline and subsequent serum fructosamine measurements were included. Serum samples were analyzed at the Neodin Veterinary Laboratory. Serum fructosamine concentrations of 360 to 450 μmol/L, 450 to 550 μmol/L, and over 600 μmol/L, it were categorized as good, moderate, and poor glycemic control, respectively.

2.3. Statistical analysis

All data were analyzed using IBM SPSS Statistics or GraphPad Prism 6 software. Basic data including insulin dose, serum fructosamine concentration, and body weight were expressed mean ± standard deviation. Serum fructosamine concentration was measured for 8 dogs in the glargine group and 5 dogs in the NPH group. Analyses of duration time and fructosamine concentration were performed by paired t-test. Relative percent body weight was analyzed by using repeated measure two-way

analysis of variance (ANOVA). Body weight at the time of switching from NPH to insulin glargine was set as the reference value. Statistical significance was defined as $p \leq 0.05$.

3. Results

3.1. Study population

From January 2009 to January 2014, 32 dogs were included in this study. Among these, 17 dogs exhibited poor glycemic control during NPH treatment and thus had their insulin therapy type switched to glargine by decision of the treating physician. The remaining 15 dogs maintained good glycemic control with NPH insulin and received this therapy for at least 1 year.

3.2. Signalments

Signalments of the glargine and NPH groups are shown in Table 1. In the glargine group, 1 of the 17 dogs (5.9 %) was an intact male, 10 (58.8 %) were neutered males, 3 (17.6 %) were intact females, and 3 (17.6 %) were spayed females. All patients in the glargine group were small breeds; 3 each of Miniature Schnauzer and Yorkshire Terrier, two each of Miniature Pinscher, Mongrel and Poodle, four Maltese, and one Spitz. Mean body

weight was 4.5 ± 1.7 kg, and mean BCS was 4.9 ± 0.9. Mean age was 8.6 ± 1.9 years. The mean diabetes duration (from time of diagnosis to March 2015) was 27.3 ± 18.9 months. Concurrent diseases included pancreatitis in 6 cases (35.3 %), diabetic cataract in 8 cases (47.0 %), bacterial cystitis in 4 cases (23.5 %), cystolith in 1 case (5.8 %) hyperadrenocorticism in 2 cases (11.7 %) and tumor in 2 cases (11.7%). Diets included 2 of table food, one of commercial dog food and 14 of prescription diet for diabetes mellitus.

In the NPH group, 2 of the 15 dogs (13.3 %) were intact males, 9 (60 %) were neutered males, 1 (6.7 %) was an intact female, and 3 (20 %) were spayed females. Their breeds were two of Yorkshire Terrier and Maltese, six of Miniature Schnauzer, and one each of Mongrel, Pug, Pomeranian, Poodles and Labrador Retriever. Mean body weight was 8.9 ± 10.2 kg and mean BCS was 5.4 ± 1.7 grade. Mean age was 9.3 ± 2.8 years, and mean diabetes duration was 17.8 ± 16.0 months. Concurrent diseases included 4 cases (26.6 %) of hyperadrenocorticism, 3 cases (20 %) of pancreatitis, 5 cases (33.3%) of bacterial cystitis, 1 case (6.6 %) of hypothyroidism, 1 case (6.6%) of Evans syndrome, 1 case (6.6%) of intervertebral disc degeneration and 1 case (6.6%) of tumor. All patients in the NPH group were being fed prescription diet for diabetes mellitus.

3.3. Effect on duration time

As shown in Figure 2, duration time was measured in both groups. In the glargine group, the mean duration time increased from 4.40 ± 0.97 hours to 6.79 ± 1.36 hours ($p<0.001$). In the NPH group, mean duration time was slightly increased from 6.20 ± 1.85 hours to 6.62 ± 1.88 hours; however, this change was not statistically significant ($p\geq0.05$). Mean duration time in the first 3 months was significantly higher in the glargine group compared to the NPH group ($p<0.001$).

3.4. Effect on body weight

Relative percent body weight was analyzed at 3-months intervals (Figure 3). In the glargine group, mean relative percent body weight at the start of study was 110.97 ± 14.4 %. Mean relative percent body weight at 3 months was 100 % (reference value). Mean relative percent body weight at 6 months was 98.52 ± 7.15 %. Mean relative percent body weights at 9 and 12 months were 99.65 ± 12.80 % and 101.92 ± 13.99 %, respectively. In the

NPH group, mean relative percent body weight at the start of study was 106.03 ± 6.79 %. Mean relative percent body weight at 3 months was 100 % (reference value). Mean relative percent body weight at 6 months was 96.25 ± 8.23 %. Mean relative percent body weights at 9 and 12 months were 94.15 ± 9.21 % and 93.98 ± 9.37 %, respectively. In both groups, the change in relative percent body weight over time was significant ($p<0.001$). The mean relative percent body weight of the glargine group was significantly higher than that of the NPH group ($p = 0.0076$).

3.5. Effect on serum fructosamine concentration

Serum fructosamine level was measured in the glargine group before and after switching insulin, and in the NPH group in the first 3 months and final 3 months of the study. In the glargine group, mean serum fructosamine concentration was 614.5 ± 146.9µmol/L before switching insulin, and 531.6 ± 51.3 µmol/L after switching (Figure 4). On the other hand, mean serum fructosamine concentration in the NPH group was 627.4 ± 94.9 µmol/L in the first 3 months of the study, and 609.8 ± 93.9 µmol/L during the last 3 months. Although the changes were insignificant in both groups ($p > 0.05$), there was a tendency toward decrease, especially in the glargine group.

3.6. Risk of hypoglycemia and ketonuria

Complications of insulin therapy were analyzed during the last 3 months of the study (Figure 4). Three patients from the glargine group (17.6%) and 3 patients from the NPH group (20.0%) had ketonuria as assessed by urinary dipstick testing. Only one patient from the NPH group had diabetic ketoacidosis, and this was well treated. No symptomatic hypoglycemia was observed by owners or physicians. One patient from the glargine group (5.9%) and two patients from the NPH group (13.3%) showed asymptomatic hypoglycemia, defined as blood glucose $\leq$ 60 mg/dL in the absence of symptoms. Insulin glargine was thus found to be as safe as NPH insulin.

3.7. Effect on the dosage

The insulin dosage was recorded whenever it was adjusted by treating physicians, and was analyzed in the first 3 months and final 3 months of the

study in both groups. In the glargine group, the mean insulin doses during NPH treatment and glargine treatment were 0.49 ± 0.19 U/kg, and 0.51 ± 0.16 U/kg, respectively. In the NPH group, the mean insulin doses during the first 3 months and final 3 months of the study were 0.43 ± 0.21 U/kg and 0.59 ± 0.32 U/kg, respectively. The differences were not statistically significant in either group. While the NPH group tended to require a higher insulin dose over time, the glargine group had a little change in insulin dose.

4. Discussion

This retrospective study was conducted to evaluate the effect of insulin glargine in 32 canine diabetes patients treated at SNU-VMTH from January 2009 to December 2014. The analysis compared the 17 dogs that were switched from NPH to glargine with the 15 dogs that continued NPH insulin therapy. Increased mean duration time and relative percent body weight, but a tendency toward decreased serum fructosamine concentrations, were observed in the glargine group. The results were similar to those of dogs that exhibited good glycemic control with NPH insulin.

The goal of insulin therapy is maintenance of a normoglycemic state. The effect of insulin therapy is regulated by many factors, including type of insulin, dose, and injection time; however, insulin type is the most important of these. Due to the development of recombinant DNA techniques for insulin synthesis, various type of insulin can now be used. As described earlier, insulin types may be classified as rapid acting, short acting, intermediate acting, or long acting, depending on properties; examples include lispro, aspart, regular, NPH, glargine, and detemir. Insulin types vary in characteristics such as onset of action, peak action, and effective

duration time. Consideration of these pharmacokinetic and pharmacodynamic properties is thus critical to select the appropriate insulin type for each patient.

Insulin replacement therapy consists of prandial insulin and basal insulin. Although NPH is one of the most commonly used types of insulin, an NPH-based basal regimen is not ideal due to short duration time and variability of absorption. In conjunction with a rapid-acting insulin, a glargine-based basal regimen may be ideal. In terms of pharmacodynamics, the onset, end, and duration of action times of insulin glargine are 1.5 ± 0.3, 22 ± 4, and 20.5 ± 3.7 hours, respectively; thus, insulin glargine has delayed absorption and a prolonged effect. A scientific review by Dewitt indicates that when adjusted clinically, insulin glargine maintains a peakless, steady state for 20 to 24 hours in most patients. In human medicine, the efficiency and safety of insulin glargine has been demonstrated in diverse studies, including retrospective and prospective studies involving various subjects such as patients with type 1 and type 2 diabetes, children and adolescents, and pregnant women. In particular, the peakless action of insulin glargine may decrease nocturnal hypoglymia. Similarly, the results of the present study indicate that in canine diabetes patients exhibiting poor glycemic control on NPH insulin, switching to insulin glargine therapy resulted in increased duration time and body weight, as well as a tendency toward

decreased serum fructosamine levels and low risk of hypoglycemia and ketonuria.

In another study, Hess and Drobatz recommended an initial glargine dosage of 0.3 U/kg SC twice daily for canine diabetes. However, this dosage is for patients receiving insulin glargine as an initial therapy. Our study suggests a glargine-based insulin regimen with an initial dose equal to that used for NPH insulin, SC twice a day after a meal, when switching from NPH insulin to glargine. In small dogs, insulin glargine was diluted 1:10 with 0.9 % normal saline, as the volume of undiluted insulin was small enough to be difficult to dispense without error. Several studies have recommended against dilution of insulin glargine because dilution of the solution may change its acidity. However, we found that there was little difference in acidity between the undiluted and 1:10 diluted insulin glargine solutions (unpublished data). When injecting the insulin glargine for small dogs, that insulin glargine was diluted 1:10 with 0.9% normal saline was recommended. In human medicine, the initial glargine dose should be 20% lower than the insulin NPH dose when switching the insulin type. However, reduction of the initial glargine dose was not necessary in this study of canine diabetes; patients received an initial glargine dose equivalent to their NPH insulin dose, and there was no evidence of hypoglycemia. In patients treated with a reduced insulin dose, glycemic control was reduced; the initial

dose of insulin glargine was subsequently adjusted to be the same as the original NPH insulin dose. We thus suggest that the initial dose of insulin glargine be the same as the final dose of NPH insulin. The duration time of insulin NPH is too short for twice-daily injection; however, with the exception of 1 dog, the treating physicians did not consider a three-times-daily regimen because of the owners' discomfort. Because of the increased duration time, switching to insulin glargine resolved the concern about the time interval between insulin injections. As the time action profile of insulin glargine and NPH insulin are certainly different, it is natural for duration time to become longer. However, these results showed the utility of administering insulin glargine in canine diabetes patients in order to make the duration time longer. Switching to insulin glargine is recommended for canine diabetes cases in which the short duration time of NPH insulin causes problems.

There are limitations to the interpretation of our data due to small sample size. It is a 6-year retrospective study. Information regarding the efficacy and safety of insulin glargine needs to be gathered over time; more time and accumulated information may help refine the insulin glargine treatment protocol. This was a short-term study, with the switch in insulin therapies occurring after 9 months. The long-term effects of switching to insulin glargine should therefore be investigated. In this study, 20% of

patients in the NPH group were extremely obese (BCS ≥ 8). Relationship between obesity and insulin resistance was doubtful. This doubt could be alleviated by performing several examinations for evaluation of insulin resistance in these patients. Furthermore, metabolic syndrome, which has attracted attention in human medicine, may also be relevant discussed in dogs.

5. Conclusion

Patients in this study exhibited adequate glycemic control after switching from NPH insulin to insulin glargine, and no safety problems were noted. These results suggest that switching to insulin glargine may be beneficial in canine diabetes patients exhibiting signs of poor glycemic control-including short duration time, ketonuria, and high serum fructosamine levels-while being treated with insulin NPH.

Table 1. Signalment of dogs with diabetes.

Charactertistics	Insulin Glargine	NPH insulin
n (%)	17 (53.1)	15 (46.9)
Sex (%)		
Intact Male	10 (58.8)	2 (13.3)
Neutered Male	1 (5.9)	9 (60)
Intact Female	3 (17.6)	1 (6.7)
Female Spayed	3 (17.6)	3 (20)
Body weight (kg)†	4.5 ± 1.7	8.9 ± 10.2
BCS (1-9)†	4.9 ± 0.9	5.4 ± 1.7
Age (years)†	8.6 ± 1.9	9.3 ± 2.8
Diabetes duration (months) †§	27.3 ± 18.9	17.8 ± 16.0

†Mean ± standard deviation.

§Diabetes duration was defined as the period from the time when canine diabetes diagnosed to 2015 March.

Table 2. Complications of patients.

Patients with complications	Glargine group (n = 17)	NPH group (n=15)
Ketonuria	3 (17.6%)	3 (20.0%)
Hypoglycemia	1 (5.9%)	2 (13.3%)

It is result of investigation the complications of three months up to the end of the study. Whenever dogs visited hospital, urinary analysis was performed with measurements of glucose curves. There is no symptomatic hypoglycemia during the study. In this table, hypoglycemia means asymptomatic hypoglycemia. The asymptomatic hypoglycemia was defined as when blood glucose level drops below 60 mg/dL without the symptoms.

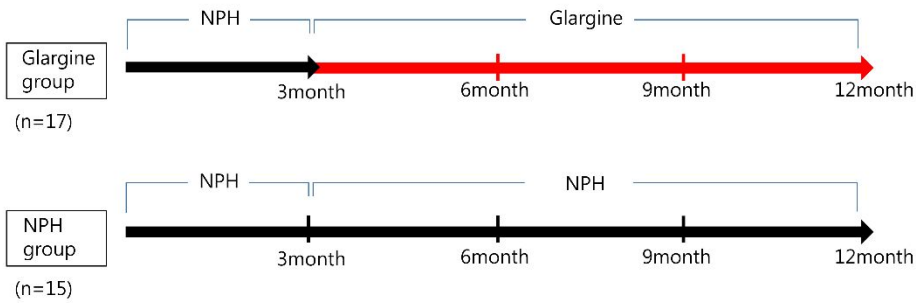

Figure1. Scheme of the retrospective study. Thirty-two dogs had been treated with NPH. Among them, 15 dogs (NPH group) received NPH insulin treatment for at least 1 year, and maintained good glycemic control. Another 17 dogs (Glargine group) were switched to glargine owing to poor glycemic control.

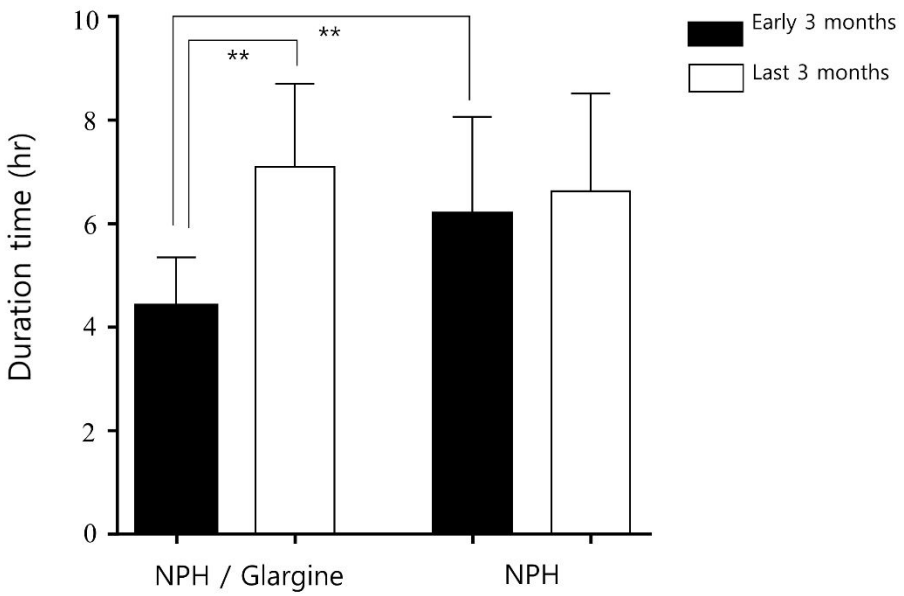

Figure 2. Mean duration time from the first 3 months of the study (when both groups were being treated with NPH insulin) compared to the final 3 months of the study. In the glargine group, the duration time was longer after switching from NPH to glargine ** ($p < 0.001$). In the NPH group, there was no significant difference in duration time. Duration time was defined as the time at which the blood glucose value rose to 250mg/dL after the nadir from fasting.

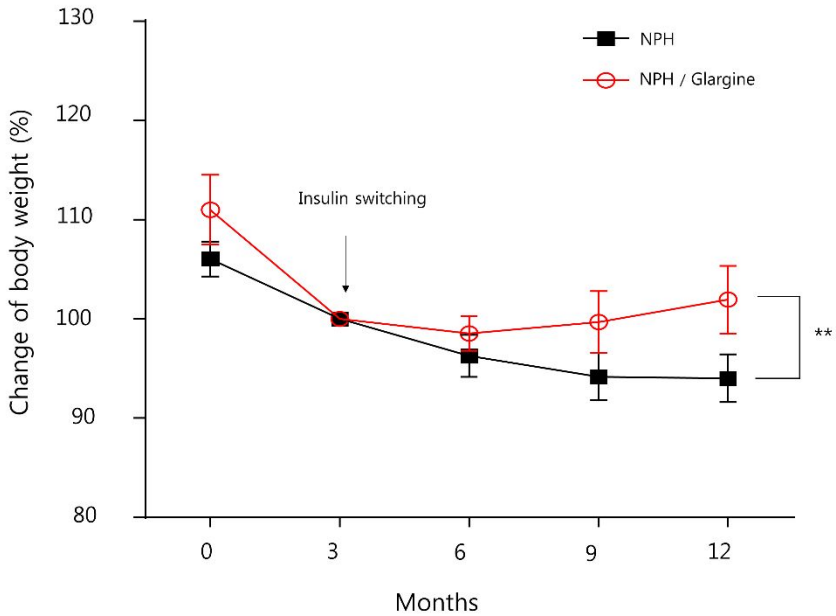

Figure 3. Comparison of mean relative percent body weight over time in the glargine and NPH groups. The reference value was set at 100%. Significant weight gain over time was observed in both groups ($p<0.0001$). Values for the two groups were significantly different** ($p = 0.0076$).

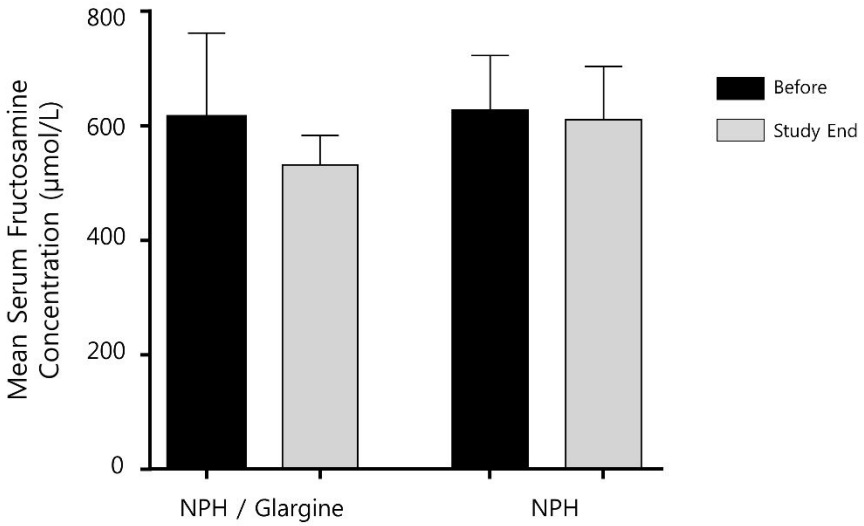

Figure 4. Comparison of mean serum fructosamine concentrations over time in the glargine and NPH groups. In the NPH insulin group(n=5), the mean serum fructosamine concentration was 627.4± 94.9 μmol/L at baseline and 609.8 ± 98.9 μmol/L at end of the study. In the insulin glargine group (n=8), the mean serum fructosamine level was 614.5 ± 146.9 μmol/L at baseline and 531.6 ± 51.3 μmol/L at the end of the study. In each group, there was no significant difference between the two time points.

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국문 초록

개 당뇨병 환자에서 인슐린 NPH로부터 인슐린 Glargine으로의 전환 효과 연구

지도 교수: 윤 화 영
서울대학교 대학원
수의학과 수의내과학 전공
이 지 예

당뇨병은 개에서도 흔한 내분비 질환 중 하나로 내인성 인슐린의 고갈로 인해 나타나므로 그 치료에 인슐린 요법이 절대적으로 중요하다. 본 연구는 개 당뇨병 환자들에서 인슐린 glargine의 당 조절 효과를 알아보기 위한 후향성 연구이다. 2009년 1월부터 2014년 1월까지 서울대학교 동물병원에서 치료받고 있는

32마리의 개 당뇨병 환자를 대상으로 진행하였다. 그 중 15마리는 1년 이상 인슐린 NPH로 치료를 받고 있었으며 적절한 당 조절을 유지하였다. 나머지 17마리는 Neutral Protamine Hagedorn (NPH)로 관리하였으나 당 조절이 잘 되지 않아 Glargine으로 인슐린 종류를 전환하였다. 모든 개 당뇨병 환자에서 신체검사를 포함한, 전혈구 검사, 혈청 화학 검사, 복부 x-ray 및 초음파, 1년 동안 주기적으로 기록된 당곡선 분석을 실시하였다. Glargine 군에서 인슐린 전환 이후 지속시간(duration time)이 54% 길어짐을 확인했다. NPH 군과 Glargine 군 모두에서 체중은 점차적으로 증가하였다. 혈청 프룩토사민(Fructosamine)은 NPH 군에서 보다 Glargine 군에서 더 크게 감소하는 경향을 보였다. 케톤뇨의 경우 NPH 군에서 20%의 환자에서 나타났으며, Glargine 군에서는 17.6%가 확인되었고, 저혈당증의 경우 NPH 군에서는 13.3%의 환자가, Glargine 군에서는 5.9%의 환자가 저혈당 증세를 보였다. 이러한 결과들은 짧은 지속시간이나 높은 혈청 fructosamine 농도, 케톤뇨증 등을 보이는 NPH로 관리받고 있는 개 당뇨병 환자들에게 인슐린 Glargine으로 전환하면 더 나은 효과를 기대할 수 있을 것이다.

주요어: Glargine; NPH; 인슐린; 당뇨; 개; 프룩토사민

학번: 2014-21946