Original Article

Effect of camel milk on glycemic control and insulin requirement in patients with type 1 diabetes: 2-years randomized controlled trial

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Abstract

Background/Objectives: Hypoglycemic effect of camel milk supplementation in experimental rat model and significant reduction in doses of insulin in type 1 diabetic patients have been observed in our previous studies. This long-term study was undertaken to assess the efficacy, safety and acceptability of camel milk as an adjunct to insulin therapy in type 1 diabetics.

Subjects/Methods: In this 2-year randomized clinical, parallel design study, 24 type 1 diabetics were enrolled and divided into two groups. Group I (*n*=12) received usual care, that is, diet, exercise and insulin and Group II (*n*=12) received 500 ml camel milk in addition to the usual care. Insulin requirement was titrated weekly by blood glucose estimation. Results were analyzed by using the regression technique.

Results: In camel milk group, there was decrease in mean blood glucose (118.58±19−93.16±17.06 mg/dl), hemoglobin A1c levels (7.81±1.39−5.44±0.81%) and insulin doses (32.50±9.99−17.50±12.09 U/day, *P*<0.05). Out of 12 subjects receiving camel milk, insulin requirement in 3 subjects reduced to zero. There was nonsignificant change in plasma insulin and anti-insulin antibodies in both the groups.

Conclusion: It may be stated that camel milk is safe and efficacious in improving long-term glycemic control, with a significant reduction in the doses of insulin in type 1 diabetic patients.

Keywords: camel milk; diabetes; adjunctive therapy; glycemic control; insulin therapy

Introduction

Camel milk has emerged as a potent therapeutic alternative, which can help in reducing insulin doses. Primary treatment of type 1 diabetes mellitus is insulin replacement. Although conventional injectable insulin therapy meets this goal, it is associated with several therapeutic disadvantages, such as hyperinsulinemia, pain and inconvenience. Many attempts have been made to find alternative methods of insulin delivery through non-invasive routes (**Owens, 2002**; **Gordberg and Gomez-Orellana, 2003**; **Cefalu, 2004**). Among the alternative routes available for insulin delivery, oral administration is the most preferable, as it offers significant advantages in terms of therapeutic efficacy and patient acceptability. As orally delivered insulin undergoes a hepatic pass before entering the circulation, it has the potential to mimic the effects of pancreas-secreted insulin in terms of inhibition of hepatic gluconeogenesis (**Lewis *et al.*, 1996**; **Clement *et al.*, 2002**). Camel milk is one such alternative, as one of its proteins has many characteristics similar to insulin (**Abu-Lehia *et al.*, 1989**), and it does not form coagulum in acidic environment, thus, safeguarding the viability of its components and making it available for absorption in intestine. Radioimmunoassay of camel milk has revealed that it contains high concentration of insulin, that is, 52.03 U/l (**Singh, 2001**) in comparison with cow milk, in which it is very low, that is, 16.32 U/l. There is significantly higher insulin (60.23 U/l) in human milk, but it is not available for absorption in intestine probably because of coagulation in stomach.

Taking all these evidences in account, a long-term study was undertaken to study the efficacy of camel milk in improving the glycemic control, consistent reduction in the doses of insulin and long-term safety profile in type 1 diabetes patients, with the aim that such an investigation would help to establish a more rational use of camel milk to control blood sugar levels in these patients.

Subjects and methods

Selection of subjects

In total, 24 type 1 diabetic subjects were randomly selected from the outpatient diabetic clinic in the PBM Hospital, Bikaner, India. The patients were advised to follow a strict diet, that is, fiber rich and low-fat diet, with 3-km daily walk and taking insulin treatment for 1 month before randomization as well as during the course of study. During this period, frequent monitoring of blood sugar was done to maintain euglycemia. After 1 month the patients were randomly divided into two groups—Group I and Group II. Allocation to the intervention and control groups was matched regarding their age and male to female ratio. Mean body mass index (BMI) for both the groups were also compared before the study and was found nonsignificantly different. Randomization was computer generated. Both the groups were also matched for duration of diabetes diagnosis and duration of insulin therapy. Group I patients (*n*=12) served as control group receiving usual care, that is, diet, exercise and insulin, and Group II patients (*n*=12) were treated as study group receiving 500 ml of camel milk supplementation daily in addition to the recommended diet, exercise and insulin for 24 months. Patients were provided camel milk daily in the morning at the research center. Information about their compliance to camel milk consumption, and diet (by 24-h recall method) and exercise was taken regularly by dietician. Patients with any acute metabolic complications like hypoglycemia, ketoacidosis, cardiovascular event, renal or acute infection were not included in the study. Patients were not allowed to take non-insulin pharmacotherapies or any other concomitant medicine throughout the study period. All the subjects randomized were non-camel milk drinker. The local ethics committee of SP

Medical College, Bikaner approved the study protocol. A written informed consent was obtained from the patients and in case of minors, from their parents.

Study design and analysis

This study was a randomized, open clinical, parallel design single-center study. Blood sugar level was measured twice a week before breakfast and before dinner, and insulin doses were titrated weekly according to mean blood sugar levels. Patients were instructed to inform immediately for any untoward event like hypo- or hyperglycemia and other complications. All patients were trained and provided with a one-touch profile memory glucometer (Lifescan, Milpitas, CA, USA), along with strips for self-monitoring of blood glucose concentrations, and were instructed to record the glucose readings and insulin doses. Vital signs, body weight, hematological and laboratory parameters, hemoglobin A1c (HbA1c) levels were monitored throughout the study. Patients were also monitored for symptoms of hypoglycemia, and glucose readings were obtained when hypoglycemic symptoms occurred. Anti-insulin antibodies detection, brucellosis agglutination test and enzyme-linked immunosorbent assay for tuberculosis were carried out annually. Safety evaluations included detail physical examinations including vital signs and laboratory parameters.

Assays

Blood sugar concentration was measured using the glucose oxidase method (**Trinder, 1969**; **Kaplan, 1984**). Plasma insulin and C-peptide were estimated by fully automated chemiluminescence analyzer (Immulite, DPC, Siemens Healthcare Diagnostics, Deerfield, IL, USA) (**Clark, 1999**). Anti-insulin antibodies were estimated by radioimmunoassay (**Desbuquois and Aurbach, 1971**). HbA1c level was measured by ion-exchange chromatography using DS-5 HbA1c analyzer (Drew Scientific Inc., Dallas, TX, USA) (**Cohen et al., 1993**).

Statistical analysis

Statistical analysis was carried out by using the SPSS version 10.0 (SPSS South Asia Pvt. Ltd, Bangalore, India). The baseline difference between the two groups was analyzed using *t*-test for independent samples assuming heteroscedastic variance. Changes from baseline to end point were analyzed using analysis of variance. The groups were taken as independent variables. Insulin dose, mean blood sugar and HbA1c were taken as dependent variables and analyzed independently. Statistical significance was assigned for *P*-values <0.05.

Results and discussion

The mean age observed in Group I and II was 14.50±8.43 and 16.67±8.89 years, respectively, (difference found was statistically nonsignificant). Male to female ratio in Group I and II was 7:5 and 10:2, respectively. The baseline characteristics of the study groups were similar in terms of BMI, fasting blood glucose, HbA1c, dose of insulin, plasma insulin, C-peptide and anti-insulin antibody (**Table 1**). After 2 years of study, improvement in BMI was observed in both the groups, which may be attributed to adolescent growth along with good glycemic control (**Table 1**). Decrease in mean fasting blood glucose levels was observed in Group II, with a significant

reduction in the doses of insulin requirement (**Table 1**, **Figure 1**), whereas in Group I there was significant increase in insulin requirement. In three diabetic patients of Group II, insulin requirement reduced to zero in the later phase of study. Improvement in HbA1c levels was found more pronounced in Group II as compared with the control group. There was significant change in C-peptide levels in both the groups, as all the patients were on insulin therapy, whereas no change was observed in plasma insulin and anti-insulin antibodies (**Table 1**). Anti-insulin antibody titers were <20% even after 2 years. No significant treatment-emergent adverse events were reported in either group. When both the groups were analyzed statistically before and after treatment to see the effect of treatment in between groups over the study period, there was a reduction in fasting blood glucose levels, HbA1c and the doses of insulin required (*P*<0.05) in camel milk group as compared with control group (**Table 1**). Acceptability to camel milk was assessed by the occurrence of hypoglycemic and untoward event. No significant hypoglycemic event as well as untoward event was observed in the group receiving camel milk, thus, showing good acceptability of camel milk.

Figure 1.
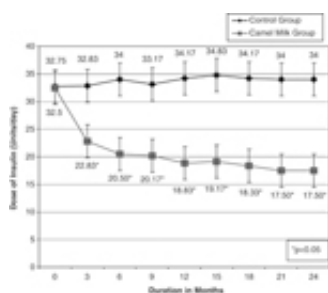
Mean dose of insulin in control and camel milk groups.

Full figure and legend (61K)

Table 1 - Effect of camel milk on biochemical parameters within groups before and after treatment among control and experimental groups of type 1 diabetic patients.

Full table

The goal of oral insulin therapy is to mimic the effects of pancreas-secreted insulin in order to control postprandial hyperglycemia and to prevent hypoglycemia between meals. In previous separate clinical trials for 3 months, 6 months and 1 year, the efficacy of camel milk causing significant hypoglycemic effect was reported when given as adjunctive therapy. This effect was presumably due to the presence of insulin/insulin-like protein and because of lack of coagulum formation of camel milk in an acidic environment (**Agrawal *et al.*, 2002**, **2003**, **2005**). The present study demonstrated that there was statistically significant improvement in mean BMI in

both the groups. In this study, all the subjects were receiving insulin, conferring in better glycemic control, which in turn improved the mean BMI.

The important observation of the present study was a significant reduction in insulin requirement (46.15%) at the end of 2 years in patients consuming camel milk, in comparison with control group. Among the 12 subjects in camel milk-consuming group, each patient had significant response to reduction in insulin requirement, but the remarkable observation was gradual reduction upto zero in three subjects. These three subjects reached to this level on 12th, 18th and 21st month of the study and returned to this 'no insulin requirement status' upto the end of the study, with some intermittent deviations. Two out of these three subjects maintained this zero level continuously, from 18th to 21st month, till the end of study. Exact reason behind reduction in insulin requirement upto zero in these three subjects is not known. However, it may be attributed to the immunopotentiating effect or improvement in β-cell function due to camel milk supplementation, as rest of the factors like diet and exercise were similar for all the subjects. Researchers, exploring the field of non-invasive insulin delivery, have been continuously making efforts to administer insulin through different systems including oral delivery. Hexyl-insulin-monoconjugate-2 is considered as the most promising oral insulin to date, with bioavailability of ~5% (**Agamy *et al.* (1992)**. The insulin-requirement-lowering effect due to camel milk supplementation in this study suggests emergence of camel milk as a new oral insulin, which can give new dimensions to the therapeutic insulin era. This may be strongly recommended, as insulin requirement reduced to zero in three diabetic subjects.

The lack of hypoglycemic events in this study is encouraging and it looks more acceptable for patients with type 1 diabetes. The promising data in this study are in consistent with study conducted by **Clement *et al.* (2002)** using oral insulin product. The significant reduction was observed in HbA1c levels in camel-milk receiving group (7.81–5.44%). HbA1c is marker of glycemic control and improvement in its values clearly indicates better glycemic control. Fasting plasma insulin levels did not reveal any significant change in each group, though significant increase in C-peptide levels in camel milk group (0.16–0.21 ng/ml) may reflect improvement in β-cell function. In our previous study, after 1 year of camel milk supplementation, the C-peptide level increased from 0.18 to 0.24 (**Agrawal *et al.*, 2005**). Fasting insulin *per se* cannot be considered as an accurate surrogate for insulin sensitivity. It can simply be reported as a quantitative reflection of insulin resistance.

Several studies have shown that patients treated with insulin, develop significant insulin antibodies after some period and these subjects occasionally experience prolongation of insulin action, which produces nocturnal hypoglycemia and insulin resistance during the day period (**Jeandidier *et al.*, 1995**). In the present study, we did not observe marked changes in the positive proportion of insulin antibodies level.

The exact cause of hypoglycemic effect of camel milk is not known. It is possibly due to insulin-like activity, regulatory and immunomodulatory function of β cells (**Lutz, 2002**). **Agamy *et al.* (1992)** found good amount of lysozyme, lactoferrin, lactoperoxidase, immunoglobulin G and secretory immunoglobulin A in camel milk. The lack of coagulum formation of camel milk may also be helpful in taking the insulin present in it unchanged to intestine where it can be absorbed even if some amount is destroyed in the passage. **Beg *et al.* (1986)** have found that amino-acid sequence of some of the camel milk protein is rich in half-cystine, which has superficial similarity with insulin family of peptides.

Anecdotal reports also suggested that camel milk consumption is associated with low prevalence of diabetes. In an epidemiological observation, **Agrawal *et al.* (2004)** studied the prevalence of diabetes and glucose intolerance in the Raica community (a desert tribe of North-west Rajasthan) consuming camel milk habitually as a part of staple diet. They reported a very low prevalence of both variables, which may be due to the protective influence of camel milk. The results of the present study are in agreement with the previous observation of positive effects of supplementation of camel milk as an adjunctive to insulin therapy in type 1 diabetic patients (**Agrawal *et al.*, 2003**, **2005**).

Despite the limited size of the study population, we were able to demonstrate a significant association between camel milk consumption and gradual reduction in insulin requirement in type 1 diabetic subjects. Further studies are needed to verify these observations. In conclusion, the results of the present study throw a light on the potential use of camel milk as an adjunct to insulin therapy, for better glycemic control and good quality of life.

Conflict of interest

The authors declare no conflict of interest.

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