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Oleoylethanolamide-based Treatment in Obesity: A Retrospective Analysis of 100 Cases from a Single Center in the Northern Territory of India

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Abstract: ***Background & Objectives: New therapeutic approaches with minimal or no adverse effects are needed to contain and counter the epidemic of obesity. Oleoylethanolamide is a bioactive lipid mediator shown to cause satiety, weight loss, and lipolysis in clinical studies. This retrospective analysis investigated the characteristics of patients initiated on the combination of oleoylethanolamide (200 mg), pantethine (75 mg) and valine (10 mg) treatment in routine clinical care and further assessed subsequent changes in weight, glycaemic and metabolic profile. Method: The analysis reviewed electronic records of 100 obese patients treated with the above combination between July 15, 2018 and December 15, 2018. Results: At the end of 3 months, daily intake of the above combination reduced the mean weight (−6.16 kg), waist circumference (−4.77 cm), total body fat (−3.14%) and BMI (−1.99 kg/m^2), significantly ($p < 0.01$). The mean values of liver enzymes (ALT, and AST) and lipid parameters (TC, TG, LDL) also reduced significantly from baseline. The daily fullness increased in 76% of patients and the cravings reduced in 85% of patients. Conclusion: The above results suggest that the combination of OEA, pantethine, and valine could be effective in suppressing appetite and controlling weight in obese people.***

Keywords: Obesity; Oleoylethanolamide; Pantethine; Valine; Appetite suppression

1. Introduction

Obesity is a rapidly growing threat to global healthcare, with >1.9 billion adults being overweight and 650 million of them considered obese[1]. National Family Health Survey-4 [NHFS-4] found 10.1% to 38.2% of the population to be obese in India.[2] ICMR-INDIAB study 2015 also reported a prevalence rate of 11.8% to 31.3% and 9.8% to 26.6% for obesity and central obesity respectively.[3] Approximately 60-70% of patients with obesity are dyslipidemic.[4] Dyslipidemia is the major contributor to atherosclerosis and consequently leads to cardiovascular disease (CVD) in obesity. The association between dyslipidemia and obesity is complicated and is directly affected by brown fat, insulin resistance and fat distribution in the body.[5]

Left untreated, obesity may lead to several diseases such as type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, heart disease, cerebrovascular disease, or cancer.[6, 7] The current medical management of obesity is mainly focused on the use of pharmacological agents that increase the level of certain hormones such as noradrenaline or serotonin in the nervous system. They are mainly responsible for the suppression of appetite or feeling of fullness. The Food and Drug Administration (FDA) has approved a number of anti-obesity agents that act on the central nervous system, such as orlistat, lorcaserin, and phentermine/topiramate. These drugs can produce adverse effects, such as oily stools, pulmonary hypertension, cardiovascular toxicity, stroke, nonfatal cardiovascular events, and neuropsychiatric issues.[8] Hence new therapeutic approaches with minimal or no adverse effects are needed to contain and counter the epidemic of obesity. One such approach is a combination of Oleoylethanolamide (OEA), pantethine and Valine (OEA+) as studies have shown the anti-obesity effect of these components.

OEA belongs to the fatty acid ethanolamide family and is a bioreactor lipid mediator. It is a structural analogue of endocannabinoid arachidonoyl ethanolamide (or anandamide) but neither binds nor activates the cannabinoid receptors.[9, 10] By activating peroxisome proliferator-activated receptor-alpha (PPAR-α) it exhibits several pharmacological effects like inducingthe feeling of fullness, loss of body weight, and lipolysis stimulation.[9-11] The affinity of OEA to PPAR-α is high and mice lacking these receptors did not show the majority of the pharmacologic effects.[10, 11] β-Aminoisobutyric acid (BAIBA) also increases β-oxidation in hepatocytes via a PPAR-α mediated mechanism.[12] Pantethine, a dimer formed by linking pantothenic acid (vitamin B5) with cysteamine, has been widely tested for lipid-lowering activity [13]. Human trials and *in vitro* studies have shown that pantethine inhibits fatty acid synthesis and HMG-CoA reductase.[13]

Given the role and association of PPAR-α and HMG-CoA reductase-mediated signalling in obesity and metabolic dysfunction, it is hypothesized that simultaneous activation of PPAR-α and blockade of HMG-CoA reductase with OEA+ can potentially ameliorate obesity and metabolic dysfunction. This retrospective analysis investigated the characteristics of patients initiating OEA+ in routine clinical care and further assesses subsequent changes in weight, glycaemic and metabolic profile.

2. Materials and Methods

Study setting and population

This is an outpatient urban facility dedicated to patients with endocrine and metabolic disorders in Northern India. OEA+ was given to individuals aged ≥18 years with obesity (defined by the Asian Indian Consensus), as an adjunct to a reduced-calorie diet and increased physical activity.

Patients were not given OEA+ if they had any of the following: a medical history of serious gastrointestinal, heart, kidney, liver, or mental diseases; any history of surgery (including gastroplasty) in previous 3 months; weight loss of more than 4 kg in previous 3 months; recent changes in smoking habits; a history of drug or alcohol abuse; consumption of other weight loss medications or systemic steroids; or if the patients were pregnant or nursing women.

Study Design and record selection

This retrospective analysis was conducted for a period between July 15 2018, and December 15 2018, by reviewing the electronic records of persons diagnosed to have obesity and who were treated with OEA+ during this period. Informed consent was not obtained as anonymised pooled retrospective data was used for this study. Records of patients were considered appropriate for inclusion in the study if they had received OEA+ as monotherapy, and whose follow up records were available for at least 3 months of its first administration. Patients with comorbid diseases were included only if their drug regimen had not been changed for 6 months before the administration of OEA+.

Retrospective Records review

Basic information such as age, sex, weight, BMI, Waist Circumference (WC) and percent of body fat were recorded. Intake of OEA+ was confirmed by interviewing the patients during their clinic visits. The primary efficacy endpoints were changes in weight and BMI from baseline post 3 months. Changes in WC and body fat composition as well as changes in cardiovascular or metabolic risk factors such as level of total cholesterol liver enzymes (SGOT, SGPT), lipid profiles (TC, TG, and LDL), fasting plasma glucose (FPG), HbA1c and creatinine, were also compared as secondary endpoints. The visual analogue scale graded 1-10 was used to assess hunger score while daily fullness and cravings were assessed subjectively through the questionnaire.

Statistical Analysis

All data extracted were analyzed using the Statistical Package for Social Sciences (SPSS) software version 17.0 (SPSS, Chicago, USA). The level of significance was set as 0.05 with 80% power. Normally distributed parameters were expressed as mean ± standard deviation, and non-normally distributed parameters were expressed as median and range. Paired t-test was used to compare continuous variables pre and 3 months post-OEA+ administration. Chi-square test was used to compare categorical variables across groups.

3. Results

100 obese patients were identified with different diseases who received the OEA+ for the treatment of obesity and followed up for at least 3 months post-treatment. Table 1 summarizes the pre-treatment characteristics of these patients. The average age of the patients was 37.33 ± 11.87 years, and the average weight, BMI, WC and fat at baseline were 86.72 ± 10.30 kg, 32.61 ± 1.87 kg/m^2, 92.96 ± 11.45 and 35.13 ± 3.26%, respectively. Mean HbA1c at baseline was 6.14% and mean FPG was 108.29 mg/dl. 42.1% and 35.1% of patients presented with hypothyroidism and diabetes, respectively followed by polycystic ovary syndrome (PCOS) in 17.5% of patients, and hypertension in 12.4% of patients.

Body Weight and Metabolic Variables

Complete cohort analysis

The mean weight at day 0 was 86.72 ± 10.30 kg, which reduced to 80.56 ± 9.87 kg after 3 months of treatment with OEA+, with mean weight loss difference of −6.16 kg (95% CI, −5.81 to −6.51 kg; P < 0.01). Similarly, WC and BMI were also significantly lesser (P <0.01) after 3 months of treatment as compared to baseline [Baseline (WC: 92.96 ± 11.45 cm; BMI: 32.61 ± 1.87 kg/m^2); 3 months (WC: 88.19 ± 6.25 cm and BMI:30.61± 1.68 kg/m^2)]. Compared with baseline, mean differences were −4.77 cm (95% CI, −2.68 to −6.86 cm) for WC and −1.99 (95% CI, −1.83 to −2.16) for BMI, respectively [Figure 1]. OEA+ also significantly reduced total body fat post 3 months of treatment (−3.14%; 95% CI, −2.11 to −4.18 %; P <0.01) (Table 2).

Diagnosis-based subgroup analysis

For subgroup analysis, 3 patients having diabetes and hypertension were considered in diabetes subgroup and 1 patient having hypothyroidism and hypertension was considered in hypothyroidism subgroup. After 3 months of treatment with OEA+ mean changes from baseline in patients with hypothyroidism (N=24), diabetes (N=20), PCOS (N=10) and hypertension (N=3), respectively, were −6.29 kg (p< 0.01), −6.60 kg (p< 0.01), −6.2 kg (p < 0.01) and −6.0 kg (p = 0.035) for body weight; −2.12 kg/m^2 (p< 0.01), −1.97 kg/m^2 (p< 0.01), −1.98 kg/m^2 (p< 0.01) and −1.63 kg/m^2 (p = 0.013) for BMI; −6.75 cm (p< 0.01), −1.95 cm (p = 0.674), -5.5 cm (p< 0.01) and -6.0 cm (p = 0.035) for WC and −3.90% (p < 0.01), −3.81% (p< 0.01), −3.15% (p< 0.01) and −3.47% (p = 0.035) for body fat.

Glycaemic Changes

Complete cohort analysis

After 3 months of treatment with OEA+, the glycated HbA1c and FPG level improved significantly compared to their baseline (P <0.01). The average HbA1c reduction was -0.23% (95% CI, 0.20-0.26; P < 0.01) in the 3 months period. In addition, the average fasting blood sugar was significantly decreased compared to that at the baseline by 11.60 mg/dL in 3 months (p< 0.01).

Diagnosis-based subgroup analysis

The subgroup analysis of diabetic patients showed a significant reduction in HbA1c (p < 0.01) and FBS (p < 0.01) levels after excluding those who had hypothyroidism, PCOS or hypertension at baseline. Mean FPG and HbA1c levels in patients with diabetes (N=20) was 123.5 ± 16.42 mg/dL and 6.83 ± 0.65%, respectively, at baseline. This reduced to

108.55 ± 10.65 mg/dL and 6.49 ± 0.53%, respectively after 3 months of treatment with OEA+. However, mean change from baseline in patients with hypothyroidism, PCOS and hypertension, respectively, were −11.42 mg/dL ($p < 0.01$), −6.60 mg/dL ($p < 0.01$) and −15.67 mg/dL ($p = 0.006$) for FPG and −0.18% ($p < 0.01$), −0.15% ($p < 0.01$) and −0.21% ($p = 0.083$) for HbA1c.

Other Metabolic Parameters: Hepatic, lipid and renal profiles

After 3 months of treatment with OEA+, the mean values of liver enzymes (ALT, AST, ALP), lipid profiles (TC, TG, and LDL) and creatinine were significantly decreased from baseline ($p < 0.01$). Table 2 summarizes these results.

Appetite and Cravings

After 3 months of treatment with OEA+, daily fullness and cravings were reduced in 76% and 85% patients; though it remains unaltered in 23% and 14% patients, respectively. At baseline, daily hunger score was 8 in 100 patients. This reduced to score 6 in 92 patients with OEA+, while 8 patients showed score 7 after 3 months of treatment.

4. Discussion

The results of this first retrospective analysis suggest that a daily intake of 200 mg OEA, 75 mg pantethine and 10 mg of valine for 3-months significantly decreased the appetite, anthropometric measures (body weight, BMI, WC, and fat mass) and metabolic variables in obese patients with different diagnosis (hypothyroidism, diabetes and PCOS). These findings are consistent with Laleh et al., in which daily intake of two 125 mg OEA capsules for 60 days significantly enhanced the expression of targeted genes of PPAR-α, decreased the desire to feed, and anthropometric measures including weight, BMI, WC, and fat mass (all $p<0.01$) in obese subjects.[14]

A crossover study involving 38 obese individuals receiving 2 capsules daily (containing 170mg N-oleylphos phatidyl ethanolamine (NOPE) and 120mg epigallocatechin-3-gallate (EGCG) in each capsule) found a significant weight loss and hip circumference reduction after the 2 months of intervention.[15]A similar result was seen in another study: daily intake of 2 capsules (85 mg NOPE and 50 mg EGCG) by healthy, overweight individuals improved dietary compliance and satiation, as well as reduced depressive symptoms after 2 months of treatment.[16]

Controlling food consumption is considered an important aspect of the management of lifestyle-related obesity.[17] OEA, an endocannabinoid produced by enterocytes upon the arrival of oleic acid containing food, plays an important role in the regulation of food intake.[18, 19] In this study, OEA+ reduced daily fullness and cravings in 76% and 85% patients, respectively after 3 months of treatment. In support of this finding, OEA when administered to rats or mice produced a dose and time-dependent inhibition of food intake. A large number of studies have shown that OEA administration has an anorexigenic effect by acting peripherally, prolonging eating latency or reducing meal size, depending on the nutritional state.[20] This effect was suggested to be mediated by PPAR-α activation in the proximal small intestine. OEA generated in the intestine binds with PPAR-α and activates the peripheral sensory systems in the vagus nerve. This conveys information to the nucleus of the solitary tract and gut peptides. These gut peptides regulate the hypothalamic integrative networks involved in controlling energy expenditure.[21, 22] The proposed mechanism of satiety was repressing level of nitric oxide synthase levels &thermogenesis.[23, 24] In addition, the anorexic effects of OEA, also attributed to the activation of the GPR-119 gene, resulted in the production of anorexic hormones such as GLP-1. It reduces food intake and increases satiety through GLP-1 receptors in the central nervous system and sensory neurons of the gastrointestinal tract.[25]

Management of dyslipidemia is often indicated in obese patients who are at an increased risk of developing cardiovascular disease. PPAR-α activation improves glucose tolerance and reduces plasma lipid and inflammatory processes.[26] Fibrate and glitazars, a classic PPAR-α and -γ receptor agonists, modulate several gene expression which leads to less monocyte recruitment and rapid lipid removal from macrophages. This also inhibits vascular smooth muscle cell migration and proliferation.[26, 27]These atheroprotective effects in addition to lipid-lowering properties are the mechanisms behind anti-atherosclerotic functions of PPAR-α agonists[27]. However, PPAR-γ agents have shown various serious adverse effects in clinical and preclinical studies. Except for saroglitazar, all PPARα/γ dual agonists have been discontinued due to cardiovascular risks, renal function impairment, and carcinogenic effects.[28] This has been due to higher PPARγ affinity than PPARα affinity of these molecules.[28]

Previous studies have shown that OEA has about 50-900 times higher-affinity for PPAR-α receptor than fibrates and that activation of this nuclear receptor accounts for most of their pharmacological actions.[11] OEA and BAIBA stimulate fatty acid uptake, breakdown, and its oxidation through activation of PPAR-α receptor.[11, 12, 29, 30] Few studies have shown that OEA induces fatty acid uptake in adipocytes by enhancing the expression of related genes such as FAT/CD36 while BAIBA increases the expression of brown adipocyte-specific genes in white adipocytes.[12, 29] In 2014, a study by Suárez et al. has shown enhanced thermogenesis with OEA by β-adrenergic-mediated pathway and upregulation of brown adipocyte in epididymal white adipose tissue. Combination of OEA (5 mg/kg) and selective adrenergic agonist increased the energy expenditure and reduced food intake, body weight gain, as well as respiratory quotient.[24]A human study has shown increased plasma BAIBA concentrations with exercise and inversely associated with metabolic risk factors.[31]

Pantethine, a natural compound, is a well-tolerated hypolipidemic agent that can decrease serum total cholesterol (TC), TG, LDL-C, apolipoprotein (Apo) A-I, and Apo-B.[32] A 16-week triple-blinded Randomised Controlled Trial (RCT) of 120 subjects with low to moderate CVD risk, treated with 600-900 mg/day of pantethine reported a decrease in LDL-C of 4 mg/dL (4%), TC of 6 mg/dL (3%), and apoB of 4 mg/dL (5%).[33] A further 16-week triple-blinded RCT on mildly hypercholesterolemic subjects

showed 11% reduction in LDL-C level with pantethine 600-900mg/day.[32]

To the best of the authors' knowledge, this is the first clinical retrospective analysis to assess the unique effects of OEA+ on anthropometric measurements, glycaemic and metabolic parameters, as well as appetite sensations in obese people. The major limitation of this analysis is the short duration and not evaluating PPAR genes involved in lipid metabolism. Although, OEA+ decreased the overall appetite and increased satiety after 3-months of intervention, its effect on eating after or during a meal could not be measured. The adverse effect and drug interaction profile were not carefully captured in patient records, limiting this information in the retrospective analysis.

5. Conclusion

Daily intake of 200 mg OEA, 75 mg pantethine and 10 mg of valine for 3-months significantly improved anthropometric measurements (weight, BMI, WC, and fat mass) and appetite sensations (hunger, desire to eat foods, and cravings for sweets decreased, and fullness increased) as well as glycaemic and metabolic parameters. Considering the many beneficial effects of OEA+ in various metabolic pathways, its use as a complementary approach to weight loss could be effective in suppressing appetite and controlling weight in obese people; however, further well-planned prospective studies are needed to confirm the current results.

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Table 1: Baseline Patient Demographics

Sr. No.	Characteristic (n = 100)	Value
1	Age (years)	37.33 ± 11.87
2	Gender (% Female/Male)	71/29
3	Weight (kg)	86.72 ± 10.30
4	BMI (kg/m^2)	32.61 ± 1.87
5	HbA1C (%)	6.14 ± 0.53
6	FBS (mg/dL)	108.29 ± 14.68
7	TC (mg/dL)	203.34 ± 35.26
8	LDL (mg/dL)	142.67 ± 22.21
9	TG (mg/dL)	159.99 ± 36.90
10	SGPT (U/L)	45.01 ± 9.94
11	SGOT (U/L)	39.06 ± 10.09
12	Creatinine (%)	0.99 ± 0.14
13	Hypothyroidism n (%)	24 (42.1)
14	Diabetes n (%)	20 (35.1)
15	Hypertension n (%)	7 (12.4)
16	PCOS n (%)	10 (17.5)

BMI: Body mass index, HbA1C: Glycated haemoglobin, FBS: Fasting blood sugar; TC: Total cholesterol, LDL: Low density lipoprotein, TG: Triglyceride, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase, PCOS: Polycystic ovary syndrome.

Table 2: Mean changes in biochemical investigations after 3 months of the treatment

	Baseline	3 months	Changes	P value
Fat (%)	35.13 ± 3.26	31.98 ± 4.91	-3.15 ± 5.20	<0.01
TC (mg/dL)	203.34 ± 35.26	179.77±24.13	-23.57±15.95	<0.01
LDL (mg/dL)	142.67 ± 22.21	123.26±20.89	-19.41±16.66	<0.01
TG (mg/dL)	159.99 ± 36.90	136.90±24.76	-23.09±32.49	<0.01
SGPT(U/L)	45.01 ± 9.94	35.32±6.65	-9.69±6.77	<0.01
SGOT (U/L)	39.06 ± 10.09	30.38±6.48	-8.68±8.99	<0.01
Creatinine (%)	0.99 ± 0.14	0.94±0.14	-0.05±0.08	<0.01

TC: Total cholesterol, LDL: Low density lipoprotein, TG: Triglyceride, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase.

Figure 1: Weight, BMI and waist circumference at baseline and after 3 months of treatment
BMI: Body mass index

Figure 2: Hunger score at baseline and after 3 months of treatment