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RECENT ADVANCES IN THE APPLICATION OF RESVERATROL TO IMPROVE HEALTH IN DIFFERENT THALASSAEMIC PATIENTS

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ABSTRACT

Resveratrol (3,4',5-trihydroxystilbene) belongs to a class of polyphenolic compounds called stilbenes. It may have numerous protective effects against age-related disorders, including renal diseases, through the activation of SIRT1. SIRT1 and NAD^+-dependent deacetylase was identified as one of the molecules through which calorie restriction extends the lifespan or delays age-related diseases, and this protein may regulate multiple cellular functions, including apoptosis, mitochondrial biogenesis, inflammation, glucose/lipid metabolism, autophagy, and adaptations to cellular stress, through the deacetylation of target proteins. In our present study we observed the administration of trans-resveratrol might effect the blood parameters, LFT, RFT and the Body weight and height evaluation according to their age of different male and female thalassaemic patients. This study we conclude that trans-resveratrol play an important role to increase the blood parameters of both Beta and Hb E- Beta thalassaemic patients. It also very effective for the liver and kidney and it play very important role in body growth.

KEYWORDS: Resveratrol, Beta-thalassemia, Hb E- Beta thalassaemia, LFT, RFT, Blood transfusion.

INTRODUCTION

Resveratrol (3,4',5-trihydroxystilbene) belongs to a class of polyphenolic compounds called stilbenes.[1] Some types of plants produce resveratrol and other stilbenes in response to stress, injury, fungal infection, or ultraviolet (UV) radiation.[2] Resveratrol is a fat-soluble compound that occurs in a *trans* and a *cis* configuration . Both *cis*- and *trans*-resveratrol also occur as glucosides (bound to a glucose molecule). Resveratrol-3-*O*-beta-glucoside is called piceid.[3]

Scientists became interested in exploring potential health benefits of resveratrol in 1992 when its presence was first reported in red wine.[4] leading to speculation that resveratrol might help explain the "French Paradox". More recently, reports on the potential for resveratrol to inhibit the development of cancer.[5] and extend lifespan.[6] in cell culture and animal models have continued to generate scientific interest.

Beta Thalassemia is an inherited disorder in which either very few or no red blood cells are produced by the bone marrow after infancy. The treatment is monthly whole blood transfusions and the use of a drug which is extremely toxic and cannot be used with children. The disease dramatically impacts the sufferers' quality of life and often results in death around the age of puberty. Because it is more common in less developed countries where it is virtually impossible for anyone other than the very wealthy to obtain regular supplies of clean whole blood for the required transfusions, the fatality rate is high. Even if the patient is able to obtain monthly transfusions and is able to afford the drugs to treat the disease, he or she is constantly anemic and lacking of energy.

Dr. Roberto Gambari, physician and molecular biologist, and well-known authority on Beta Thalassemia, at the University of Ferrara, discovered that Transmax resveratrol, the concentrated pure resveratrol supplement used by researchers in most clinical trials, was able to stimulate the production of embryonic red blood cells, the type that are produced when a baby is still in the mother's womb, but soon after birth cease being produced. This is an extremely important finding and one that has led to a human clinical trial now underway at the University of Ferrara. The subjects in this clinical trial are hospitalized, adolescent Beta Thalassemia patients. Hopefully resveratrol will give a new lease on life to those who suffer a disease that the pharmaceutical companies do not consider potentially profitable enough to develop a new drug for.

There is not a single study done on patients of India, where we have seen very good HU-responders (though in 50% of cases) but there are still non-respoders of HU cases. Since Resveratrol has been demonstrated to inhibit ribonucleotide reductase with an efficiency higher than Hydroxyurea (HU).[7] and Rodrigue et al.[8] found that resveratrol possesses similar properties to HU toward erythroid differentiation. They firmly demonstrated that resveratrol induces differentiation of K562 cells and augmentation of HbF in erythroid precursor cells isolated from eight sickle cell patients. Hence we want to do a study on this.

MATERIALS AND METHODS

Study groups

Patients with HPLC-screened documented Sickle cell anaemia, S-beta thalassemia, beta thalassaemia, HbE thalassaemia, HbE-beta thalassaemia, HPFH genotypes have been considered in this primary analysis.

Collection of Sample: Sample was collected from OPD of Thalassaemia Foundation, Kolkata. Total 600 patients were evaluated. Among which 456 patients with Hb-E-beta and 130 patients with Beta and HPFH and 14 patients with other hemoglobinopathies were observed.

Fetal hemoglobin studies

Hb variants' (HbA / HbA2 / HbF & others) levels was estimated by HPLC (High Performance Liquid Chromatography) (Bio-Rad, USA). Estimation of HbF was also done by using HPLC method.

Biochemical Analysis

Renal Function test (Creatinine /Urea / Uric Acid Concentration), Liver Function test (Bilirubin /Serum Alanine aminotransferase (ALT) concentration / Serum Aspartate aminotranseferase (AST) concentration) was performed by Biochemical Analyser [Microlab 300, EMerck].

RESULT

Table-1: Different blood parameters and their pre-treatment and post-treatment values in Beta thalassaemia patients.

Blood Parameters	Control Initial	Control Final	Pre Therapy	Post Therapy
HbF (%)	82.5±1.36	83.6±2.30	25.36±2.36	55.69±2.36*
HbA2 (%)	4.8±1.20	4.2±1.30	9.4±2.60	6.34± 1.25 *
HbA (%)	60.23±2.36	62.35±1.20	6.36±3.60	10.32± 2.36 *
Hb (g/dl)	7.8±2.30	8.5 ±0.25	5.26 ±1.77	8.82 ±2.31 *
MCV (fl)	80.2±2.36	83.4 ±1.36	71.68±2.39	79.44 ±1.07 *
MCH (pg)	31.0±1.23	32.0±0.69	24.48± 2.30	27.84±1.08 *
MCHC (g/dl)	38.7±1.36	38.4 ±2.36	32.66±2.49	37.06±2.07 *
Rdw (%)	16.6±1.25	16.36±1.20	25.36±1.20	22.5±2.57 *
Hct (%)	38.9±0.56	41.6±1.30	28.6 ±2.86	31.36±1.55 *

Standard deviation was done in all the result, *Significant at P<0.05 against Control Final.

Table-2: Different blood parameters and their pre-treatment and post-treatment values in Hb E-beta thalassaemia patients.

Blood Parameters	Control Initial	Control Final	Pre Therapy	Post Therapy
HbF (%)	38.94±1.77	52.2±1.50	30.6± 01.36	39.18±5.01*
HbA2 (%)	53.44±1.48	43.4±1.25	44.76±5.83	55.34±4.59 *
HbA (%)	4.74±3.32	4.4±1.30	3.72±1.47	7.57±2.70 *
Hb (g/dl)	8.61±0.93	8.31±1.03	5.87±1.17	7.17±0.89 *
MCV (fl)	63.31±1.60	63.25±1.78	62.83±2.75	65.28±1.25 *
MCH (pg)	22.86±2.59	23.5±2.92	20.72± 2.64	25.87±1.72 *
MCHC (g/dl)	36.1±0.77	35.91±0.46	32.78±0.58	35.56±1.98 *
Rdw (%)	15.45±1.68	15.9±1.57	25.36±2.61	20.40±2.26*
Hct (%)	40.36±2.69	42.36±3.07	32.36±0.72	36.23±1.53*

Standard deviation was done in all the result, *Significant at P<0.05 against Control Final.

Table-3: Evaluation of the effect of Liver Function Test (LFT) of Beta thalassaemic patients on Trans-Resveratrol Therapy.

LFT Parameters	Control Sample	Pre-treatment	Post-treatment
Bilirubin (mg/dl))	1.50±0.5	4.56±1.25	2.13±2.5*
AST (U/l)	<30	25.36±1.10	22.23±3.6*
ALT (U/l)	<40	36.56±1.12	32.63±3.5*
Total Protein (g/dl)	5.8-8.6	2.56±1.36	4.87±0.5*

***Standard deviation was done in all the result, *Significant at P<0.05 against Control.**

Table-4: Evaluation of the effect of Liver Function Test (LFT) of Hb-E Beta thalassaemic patients on Trans-Resveratrol Therapy.

LFT Parameters	Control Sample	Pre-treatment	Post-treatment
Bilirubin (mg/dl))	1.50±0.5	4.65±1.56	2.02±2.3*
AST (U/l)	<30	32.36±1.11	21.69±2.5*
ALT (U/l)	<40	35.36±0.98	29.63±6.3*
Total Protein (g/dl)	5.8-8.6	2.50±1.14	5.36±1.0*

***Standard deviation was done in all the result, *Significant at P<0.05 against Control.**

Table- 5: Evaluation of the effect of Renal Function Test (RFT) of Beta thalassaemic patients on Trans-Resveratrol Therapy.

RFT Parameter	Control Sample	Pre-treatment	Post-treatment
Creatinine (mg/dl)	0.7±0.3	4.12±1.23	1.51±0.90*
Urea(mg/dl)	6.8±3.20	18.36±1.30	12.36±2.3*
Uric Acid (mg/dl)	5.36±2.36	16.23±1.20	9.36±2.36*

***Standard deviation was done in all the result, *Significant at P<0.05 against Control.**

Table- 6: Evaluation of the effect of Renal Function Test (RFT) of Hb E-beta thalassaemic patients on Trans-Resveratrol Therapy.

RFT Parameter	Control Sample	Pre-treatment	Post-treatment
Creatinine (mg/dl)	0.7±0.3	3.6±1.23	1.8±0.90*
Urea(mg/dl)	6.8±3.20	12.36±1.30	10.36±2.3*
Uric Acid (mg/dl)	5.36±2.36	13.23±1.20	8.36±2.36*

***Standard deviation was done in all the result, *Significant at P<0.05 against Control.**

Body Growth Analysis

The Body weight and height evaluation according to their age of total 600 male and female thalassaemic patients with pre and post-treatment of trans- resveratrol therapy were clearly depicted in [Chart-1],[Chart-2],[Chart-3] and [Chart-4].

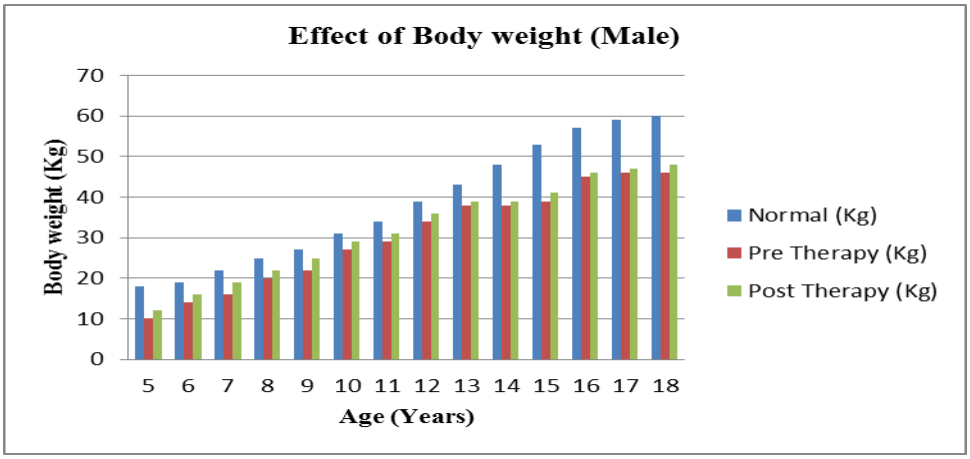

Chart 1: Effect of Body weight in male Thalassaemic Patients on Trans Resveratrol Therapy.

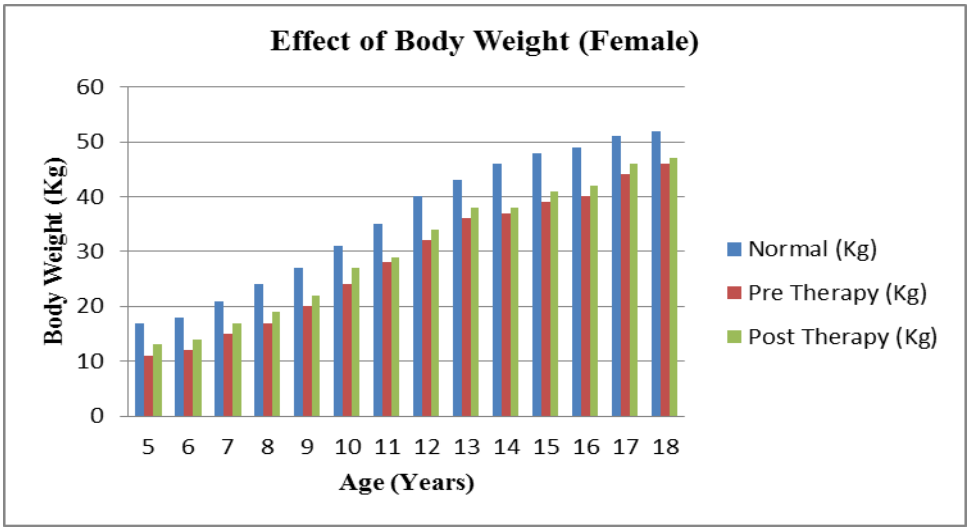

Chart 2: Effect of Body weight in female Thalassaemic Patients on Trans Resveratrol Therapy.

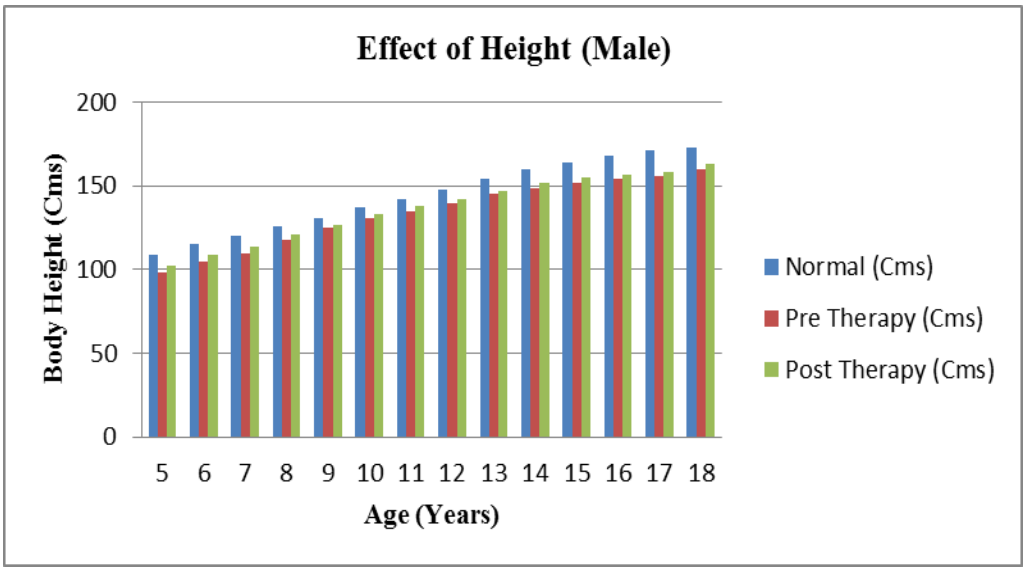

Chart 3: Effect of height in male Thalassaemic Patients on Trans Resveratrol Therapy.

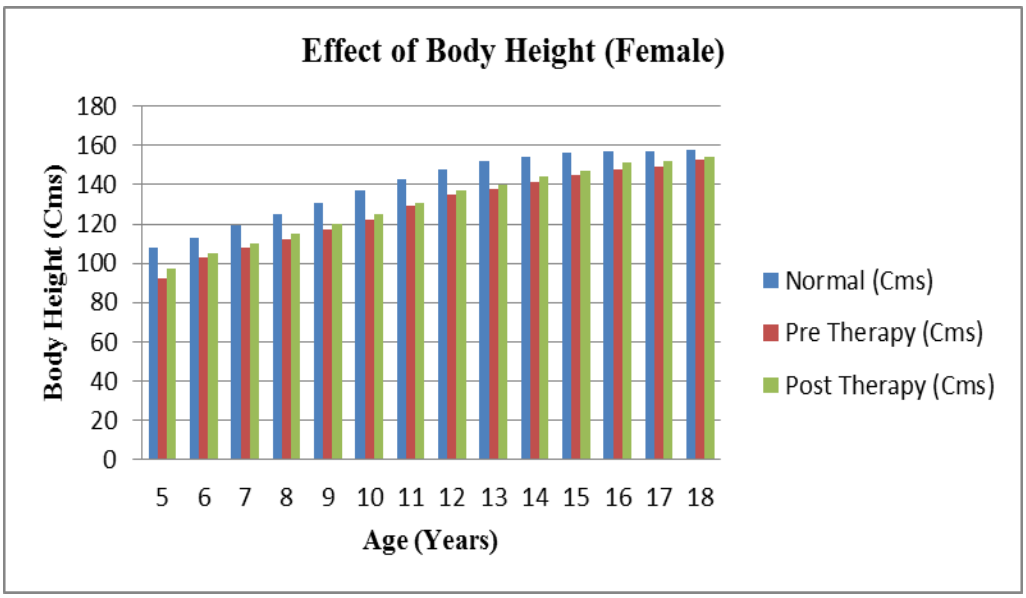

Chart 4: Effect of height in female Thalassaemic Patients on Trans Resveratrol Therapy.

DISCUSSION

Since Resveratrol has been demonstrated to inhibit ribonucleotide reductase with an efficiency higher than HU.[7] Rodrigue et al.[8] found that resveratrol possesses similar properties to HU toward erythroid differentiation. They firmly demonstrated that resveratrol induces differentiation of K562 cells and augmentation of HbF in erythroid precursor cells. Comparative analyses demonstrated that resveratrol, as HU, inhibits intracellular adhesion molecule-1 (ICAM-1) and VCAM-1 expression by endothelial cells. In addition, resveratrol possesses other properties similar to HU, including induction of nitric oxide synthase in cultured pulmonary endothelial cells and inhibition of human platelet aggregation in vitro. Interestingly, resveratrol exhibited minimal toxicity on normal hematopoietic cells, as suggested by Cle´ment et al.[9] The resveratrol is a strong inducer of HbF and a selective stimulator of the expression in β-globin genes. Again, since the effect of Resveratrol on thalassaemics is not completely understood by large number of applications and we have a very good number of patients who have not responded on HU therapy though patients having all the positive factors in their genetic background (one of which is already possessing high HbF conc. in their RBCs) known yet today, hence we want to study the genotypes of patients who responded on resveratrol but previously not on HU. So the hypothesis is that to find the extra/different molecular background for which the patients can get an benefit may be in their increase of haemoglobin conc (MCH) or in having a betterment in the RBC morphology.

In table 1and table 2 we observed the administration of trans-resveratrol the different blood parameters and their pre and post-treatment values in Beta and Hb E-Beta thalassaemic patients. Here we showed that post-treatment values are always higher than the pre-treatment values which are near about to the normal values.

In table 3, 4, 5 and 6 we observed the changes in LFT and RFT parameters during the administration of trans-resveratrol therapy. In each table we showed that post-treatment values are always higher than the pre-treatment values which are near about to the normal values.

During the administration of trans-resveratrol therapy we also observed the growth parameters according to their age of different male and female thalassaemic patients. In [Chart-1],[Chart-2],[Chart-3] and [Chart-4] we clearly depicted the body weight and height according to their age of total 600 male and female thalassaemic patients with pre and post-treatment of trans- resveratrol therapy. The post-treatment results are always better than the pre-treatment.

CONCLUSION

Resveratrol can play a pivotal role in prevention and treatment of liver disorders. It could reduce the hepatic fibrosis and hepatic steatosis through modulating the insulin resistance and lipid profile in animals. The potential therapeutic implication of Resveratrol in liver disorders especially those with hepatic steatosis. Additional carefully designed, mechanistic based, laboratory, and clinical studies need to be undertaken to provide scientific evidence for the efficacy of it in treatment of liver disorders especially those with hepatic steatosis and fibrosis. Resveratrol can also protective effects against both acute and chronic kidney injuries through its antioxidant effects and ability to activate SIRT1. It should be a useful additional treatment for preventing renal injury. However, it remains unclear whether resveratrol has beneficial effects on kidney diseases in humans and other animal models of renal diseases. In addition, a number of recent studies indicate that many of the protective effects of resveratrol could be mediated by SIRT1-independent mechanisms. It can activate the mammalian target of rapamycin (mTOR) signaling pathway which is involved in the pathogenesis for several kidney diseases, such as diabetic nephropathy.[10-12] and the autosomal dominant polycystic kidney disease.[13] Liu et al. reported that RSV increases the association between mTOR and the DEP-domain-containing and mTOR-interactive protein (DEPTOR), an identified negative regulator of mTOR.[14] Therefore, resveratrol is expected to protect the kidney by the inhibition of mTOR pathway. Further studies are necessary to verify the beneficial effects of this compound in humans and other animals of kidney diseases and to clarify the detailed mechanism for the renal protective effect of resveratrol.

In our present study we conclude that trans-resveratrol play an important role to increase the blood parameters of both Beta and Hb E- Beta thalassaemic patients. It also very effective for the Liver and kidney functions. During the administration of trans-resveratrol therapy the post-treatment values were very satisfactory than pre-treatment values. The other hand it also very effective for the body growth (Height and Weight). At the end Resveratrol is very effective medicine for both Beta and Hb E- Beta thalassaemic patients.

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Data Sharing Statement: We cannot share any unpublished data with other laboratory or person.

Patients Consent Statement: The signed consent from all the patients were taken before test was performed and kept them as official documents. In case of any unusual condition it will be presented in front of the concerned person.

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