Experimental Research

# Stem cell therapy for type1 diabetes with transplantation of stem cells into the Omental pouch, peritoneum, and blood, experimental study

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## ARTICLE INFO

## ABSTRACT

*Introduction:* Type 1 diabetes is a dreadful autoimmune disease of childhood with incidence of 0.26/1000 children in India. To develop a new, cheap, and effective treatment for this disease, we invented an autologous Stem cell therapy for type 1 diabetes in which stem cells are transplanted into the Omental pouch, peritoneum, and blood. The Omental pouch stem cell operation in the therapy is reported for the first time in the medical literature.

*Materials and methods:* Last 5 years I treated 21 patients of Type 1 diabetes with autologous stem cell therapy and in the same period, a group of 26 patients of Type 1 diabetes with conventional treatment of Insulin injections was put as a control group. Blood sugar fasting and post prandial, Anti Gad antibody titer, Glycosylated Hb and C peptide levels and weight of patient and total Insulin requirement in 24 h were the variables to be measured before the therapy and after the therapy. Stem cells were harvested from patients own bone marrow and separated by density gradient method. An infusion of 20 mg/kg methylprednisolone in 100 ML normal saline given intravenously over 1 h prior to the therapy. The total average numbers of cells harvested were $7.86 \times 10^7$. One third quantity of isolated stem cells were put into the Omental pouch through no. 7 IFT, another one third into peritoneal cavity through no. 10 IFT and remaining third is given IV in 100 ml normal saline.

*Results:* The minimum follow up was 6 months and maximum of 4 years. In the therapy group, the average weight gain after one year of therapy, daily requirement of Insulin and its drop after therapy, drop in HbA1c levels, drop in fasting and post prandial blood sugar, rise of C peptide levels and drop in Anti-GAD antibody titer were measured and was found to be statistically highly significant. The same parameters were measured in control group and was not statistically significant. There were a few side effects noted after stem cell therapy such as mild skin rash, nausea, and pain in abdomen.

*Discussion:* In autologous bone marrow derived stem cell therapy, cells are transplanted into the Omental pouch, peritoneum, and blood. Cells transplanted in the Omental pouch get vascularized like a split skin graft. Omental surface has far less cellular immunity than blood, hence, if some of these cells get converted into Islets like cells producing Insulin, then they are less vulnerable to damage by the immune system. It means that the Omental pouch may act as a new biological pancreas producing Insulin. Stem cells injected intravenously reach the pancreases and may get differentiate into Islet like cells due to specific growth factors released by pancreas. Stem cells can reverse autoimmunity by their immunomodulatory function. Stem cells transplanted in peritoneum grow longer due to large surface area and little cellular immunity and secrete growth factors and cytokines for a long time which can rejuvenate existing Islets of Langerhans. The therapy group had substantially good results compared to the control group and the difference was statistically highly significant.

*Conclusions:* Autologous stem cell therapy was safe, and effective for the long term for the treatment of Type 1 diabetes. We need a greater number of cases and a longer follow up to make it better. The therapy creates a lot of hope for Type 1 diabetes patients as it can be easily repeated any number of times.

## 1. Introduction

Type 1 diabetes is a dreadful autoimmune disease of childhood with incidence of 0.26/1000 children in India [1]. Currently insulin injection and islet cell transplantation are the FDA approved treatments. Taking multiple insulin shots daily and its cost are both unacceptable to most of

the children. Islet cell transplantation is exorbitantly costly and gives relief only for 2–5 years [2]. Medical literature has many promising animals and in Vitro studies published where stem cells have established euglycemia in diabetic rats. We need to bring the findings of animal studies on human side for the welfare of Type 1 diabetes patients. A new, cheap, and effective method needs to be developed for the treatment of this disease. There are different benefits of implanting stem cells in various parts of the body by different routes. Hence, we invented autologous bone marrow derived stem cell therapy for type 1 diabetes with transplanted of stem cells into the Omental pouch, peritoneum, and blood which gives the benefits of all 3 methods to the patient. The Omental pouch operation is reported for the first time in the medical literature (see Fig. 1).

## 2. Materials and methods: study design

Last 5 years I treated 21 patients of Type 1 diabetes with stem cell therapy in which autologous bone marrow derived stem cells were implanted into an Omental pouch, peritoneum, and blood. Age range in the therapy group was 3.5 years to 38 years. In the same period, a group of 26 patients of type 1 diabetes with conventional treatment of Insulin injections was put as a control group. Patients were distributed in both the groups in a random way. The primary objective of the study was to document any adverse events and establish the safety of the intervention. The secondary objective of the study was to evaluate the effects of the intervention on symptoms of type 1 diabetes, Insulin requirement, blood sugar and HbA1c levels, C peptide levels and autoimmunity.

## 3. Participants eligibility criteria and recruitment

Patient selection was based on World Medical Association Helsinki Declaration for Ethical Principles for medical research [3] involving human subjects. A written informed consent was obtained from the parents of all patients. Patients were diagnosed as type 1 diabetes [4] clinically based on following criterion. Most patients had a small age at the time of diabetes with presentation as ketoacidosis and severity of symptoms such as severe weight loss, extreme weakness and with polyuria and bed wetting. On investigations, most of the patients had high sugar levels more than 200 mg/dl with high HbA1c levels. Almost all had very low C peptide levels indicating a very low endogenous Insulin production. Higher than normal Anti-Gad antibody levels were objective evidence of autoimmunity, although was not seen in all patients. All the patients were Insulin dependent since the onset of the disease. The exclusion criteria were presence of acute infections such as HIV/HBV/HCV, malignancies, bleeding tendencies, renal failure, severe liver dysfunction and other acute medical conditions such as respiratory infection and pyrexia.

## 4. Preintervention assessment

An informed consent was taken from the parents of all the patients. Prior to intervention, all the patients underwent a thorough clinical examination with serological, biochemical, and hematological tests. Blood sugar fasting and post prandial, Anti Gad antibody titer, Glycosylated Hb and C peptide levels and weight of patient and total Insulin requirement in 24 h were the variables to be measured before the therapy and afterwards at every 3 monthly intervals.

## 5. Institutional ethical committee clearance

[5,6] Institutional Ethical Committee (IEC) permission taken, and institutional Committee for Stem Cell Research (IC-SCR) established at city level for peer review of stem cell research and its permission taken for the study. Special informed consent was taken from all patients/relatives.

## 6. Patient symptomatology

In the therapy group, 5 patients (23.8%) presented with significant weakness, 15 patients (71.4%) had significant weight loss, 7 patients (33.33%) had polyuria, 6 patients (28.57%) had polyphagia, 3 patients had blurred vision with vision loss (14.2%),3 patients (14.2%) had peripheral neuropathy and 2 patients (9.5%) complained of erectile dysfunction. 3 patients (14.2%) had presented as diabetic ketoacidosis with coma. Only 6 patients (28.5%) had auto immunity with significantly raised Anti Gad antibody levels.

## 7. Bone marrow harvesting

Patients below 18 years were given general anesthesia. Whereas patients above 18 years, spinal anesthesia was given. 100–150 ml marrow was aspirated using a Jamshidi bone marrow aspiration needle attached to a disposable 50 ml syringe with heparin sodium as anticoagulants from posterior inferior iliac spine.

## 8. Separation protocol for isolation of stem cells

[7] The collected bone marrow e.g., 25 ml is diluted with equal quantity of Dulbecco's Phosphate Buffered Saline with 2% Fetal Bovine Serum (PBS + 2% FBS) (Sigma-Aldrich, USA). The diluted bone marrow is poured over equal quantity of density gradient such as Lymph prep (Stem cell technologies, Vancouver, Canada) with density of 1.077 g/mL into disposable centrifuge tubes of 50 ml capacity. The tubes are centrifuged at $800 \times g$ for 20 min at room temperature (15 °C - 25 °C) with brake of. The tubes have a buffy coat at the middle containing mononuclear cells with stem cells. The buffy coat is aspirated and kept ready for infusion. A sample of this was sent for cytology to measure stem cell viability by Trypan blue and to measure stem cell count. The mononuclear cells were checked for viability (average viability count was found to be 97.3%. The average numbers of cells harvested were $7.86 \times 10^7$.

## 9. The technique of the omental pouch stem cell operation

A small incision is taken within the umbilicus and the sheath cut open to open peritoneal cavity. Omentum identified and taken out of the umbilical incision. Omental pouch was created by making a sack of the Omentum with continuous interlocking sutures of 3-0 Vicryl sutures. No. 7 infant feeding tube (IFT) is placed into it the Omental pouch (Figure: 1) and the tube fixed with a purse string suture of 3-0 Vicryl. Another no. 10 IFT is put into the peritoneal cavity. The omental pouch was placed



**Figure:1.** Showing the Omental pouch with no. 7 infant feeding tube.

inside peritoneal cavity and the sheath sutured with 1-0 Proline interrupted stitches.

## 10. Mode of transplantation of stem cells

An infusion of 20 mg/kg methylprednisolone in 100 ML normal saline started intravenously over 1 h before transplanting stem cells. The average numbers of cells transplanted were 7.86 × 107. One third quantity of isolated stem cells were put into the Omental pouch through no. 7 IFT, another one third into peritoneal cavity through no. 10 IFT and remaining third is given IV in 100 ml normal saline.

## 11. Post stem cell transplantation therapy

Patients were examined regularly for any adverse effects of the therapy. The vitals such as pulse, blood pressure, respiration monitored regularly. Blood sugar fasting and post prandial was regularly monitored by glucometer and a daily chart maintained.

## 12. Outcome measures

To assess the safety of the intervention, outcome measures were used to monitor any major or minor adverse events through the entire duration of follow up. Patients were counseled regarding the probable adverse events during informed consent. Recording of adverse events during the hospital stay was done by a health professional whereas after discharging it was recorded, as reported by the parents or primary care givers and patients diabetologists in their local area.

## 13. Monitoring procedure related adverse events

Acute procedural adverse events, associated with cell aspiration and injection, were stringently monitored over 5–7 days after intervention. Body temperature, blood sugar fasting and post prandial, blood pressure, respiratory rate, and heart rate were recorded at regular intervals. Aspiration and transplantation sites were examined every day for pain, bleeding, and signs of infection. Signs and symptoms of any anesthesia complications, headache, nausea, and vomiting were checked regularly. All the minor acute procedural adverse events were treated medically prior to the discharge of the patients from the hospital.

## 14. Monitoring cellular transplantation related adverse events

During the stay in the hospital, signs and symptoms of any allergic reaction were monitored at regular intervals. Long term major and minor adverse events were monitored to establish the safety of stem cell transplantation.

## 15. Monitoring the effects after intervention

The sugar levels were regularly monitored daily by glucometer and the dose of insulin adjusted accordingly. Blood sugar fasting and post prandial, Anti Gad antibody titer, Glycosylated Hb and C peptide levels, patient's weight and total daily Insulin requirement were the variables to be compared. These parameters were checked before the therapy and afterwards at every 3 monthly intervals.

## 16. Statistical analysis

The demographic data for all the patients was recorded and analyzed. Mean age in years at the time of intervention, mean age in years at the time of diagnosis, and mean time duration in months at which the patients were followed up were calculated. The pre- and postintervention scores predetermined level of significance at 0.05 and 0.01. Percentage analysis was conducted for the blood sugar fasting and post prandial, Anti Gad antibody titer, Glycosylated Hb and C peptide

levels, patient's weight, and total daily Insulin requirement before and after one year of the therapy in both groups. The whole statistical analysis was done in Microsoft Excel program. Statistical hypothesis testing was performed to prove statistical significance to check if the results are better in therapy group by sampling error and by mere chance or by its own merit, thus rejecting the null hypothesis (see Table 1).

## 17. Results

The minimum follow up was 6 months and maximum of 4 years. It took 3 months to see the results. The sugar levels were regularly monitored daily by glucometer by the parents and the dose of insulin adjusted accordingly by the patient's physician. Blood sugar fasting and post prandial, Anti Gad antibody titer, Glycosylated Hb and C peptide levels, patient's weight and total daily Insulin requirement were the variables to be compared. These parameters were checked before the therapy and afterwards at every 3 monthly intervals. The clinical results were completely expressed at the end of one year from the therapy. Hence, the above variables were compared at the end of one year from the therapy date (Table 1). Some patients did not send investigation reports at 3 monthly intervals due to variety of reasons such as lack of affordability, lack of motivation, lack of availability in their local area of residence etc. Weight gain is an important prognostic indicator in type 1 diabetes. Weight just before therapy and one year after therapy was measured in both groups. In the therapy group, the average weight gain after therapy was about 16% which came as statistically highly significant with $P < 0.01$ (Chart A). In the control group, the average weight gain was just 2.23% and the difference was not statistically significant (Chart B).

At the end of one year, in the therapy group, 3 (14.28%) patients went off Insulin and are free of insulin till three years after therapy. Remaining 19 (85.72%) patients average insulin requirements dropped by 51.68% after one year of therapy and the difference came as statistically very significant with $P < 0.01$ (Chart C). In the control group, no patient went off Insulin and only 13.2% patient's Insulin requirements were lower than before, and the difference was not significant statistically (Chart D). 58.6% patients Insulin requirements were the same and 28.2% patients Insulin requirements were higher than before.

HbA1c levels has an average drop of 35.78% drop in the therapy group and the difference came as statistically very significant with $P < 0.01$ (Chart E). The control group had an average drop of only 8.2% and the difference was not statistically significant (Chart F), 62.6% patients had same levels and 29.2% patients had levels higher than before.

There was an average drop of 42.8% in fasting blood sugar in therapy group and the difference was statistically highly significant with $P < 0.01$ (Chart G). In the control group, there was an average drop of 8.1% in fasting blood sugar levels and the difference was not statistically significant (Chart H). 59.3% patients had the same fasting blood sugar, and 32.6% patients had a higher post prandial blood sugar level.

There was an average drop of 50.93% in post prandial blood sugar in therapy group and the difference was statistically highly significant with $P < 0.01$ (Chart I). In the control group, there was an average drop of 13.1% in post prandial blood sugar levels and the difference was not statistically significant (Chart J). 5.3% patients had the same post prandial blood sugar, and 31.6% patients had a higher post prandial blood sugar level.

There was an average increase of 89% C peptide levels in therapy group and the difference was statistically highly significant with $P < 0.01$ (Chart K). In the control group, there was an average increase of 11.1% in C peptide levels and the difference was not statistically significant (Chart L). 65.1% patients had the same C peptide levels, and 23.8% patients had a higher C peptide level.

In the therapy group, 6 patients had a higher-than-normal Anti-GAD antibody titer which dropped to about 67% in one year indicating partial reversal of auto immunity (Chart M). In the control group, 11 patients had a higher-than-normal Anti-GAD antibody titer and only 13.8% of

**Table 1**
Patient data table.

| Sr. No | Date of therapy | Age (Yr) | Sex | History | Clinical features | Investigations Before therapy | Insulin before therapy (IU) In 24 h | Side effects of therapy | Clinical Improvement 1-year after therapy | Units of Insulin after therapy in 24 h | | | | | Investigations After therapy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr |
| 1 | August 04, 2017 | 20 | M | KCO type 1 diabetes for 2 years | Weakness, Peripheral neuropathy Weight 51 kg | Hba1c 9.1 Blood Sugar F 210 Blood Sugar pp 320 C peptide 0.05 Anti-Gad antibody 23.7 | 45 | Skin rash | Weight gain of 9 kg in 1-year, peripheral neuropathy symptoms disappeared completely | 30 | 20 | 20 | 20 | 20 | Hba1c 8.1 Blood Sugar F 186 Blood Sugar pp 210 | Hba1c 7.3 Blood Sugar F 156 Blood Sugar pp 185 C peptide 0.15 Anti-Gad antibody 11.6 | Hba1c 7.4 Blood Sugar F 162 Blood Sugar pp 190 | Hba1c 7.3 Blood Sugar F 152 Blood Sugar pp 175 | Hba1c 7.4 Blood Sugar F 160 Blood Sugar pp 185 |
| 2 | October 13, 2017 | 15 | M | KCO type 1 diabetes for 1 year | Weakness, Bed wetting, Peripheral neuropathy, Weight 53 kg | Hba1c 12.4 Blood Sugar F 310 Blood Sugar pp 452 C peptide 0.01 Anti-Gad antibody 13.7 | 70 | nil | Weight gain of 7 kg in 1-year, peripheral neuropathy symptoms disappeared completely, bed wetting completely stopped | 50 | 35 | 35 | 35 | 35 | Hba1c 8.3 Blood Sugar F 185 Blood Sugar pp 258 C peptide 0.15 | Hba1c 8.1 Blood Sugar F 180 Blood Sugar pp 252 C peptide 0.15 Anti-Gad antibody 13.7 | Hba1c 8.2 Blood Sugar F 175 Blood Sugar pp 252 | Hba1c 8.1 Blood Sugar F 170 Blood Sugar pp 248 | Hba1c 8.2 Blood Sugar F 175 Blood Sugar pp 262 |
| 3 | November 29, 2017 | 5 | M | KCO type 1 diabetes for 6 months | HO of diabetic ketoacidosis with coma, polydipsia, Weight 16 Kg | Hba1c 9.5 Blood Sugar F 226 Blood Sugar pp 358 C peptide 0.5 Anti-Gad antibody 5.47 | 12 | Pain in abdomen | Weight gain of 4 kg in 1-year, improved energy, polydipsia disappeared completely | 6 | 0 | 0 | 0 | 0 | Hba1c 5.3 Blood Sugar F 91 Blood Sugar pp 98 C peptide 0.58 | Hba1c 5.0 Blood Sugar F 73 Blood Sugar pp 78 C peptide 0.98 | Hba1c 5.1 Blood Sugar F 89 Blood Sugar pp 92 | Hba1c 5.2 Blood Sugar F 94 Blood Sugar pp 98 | Hba1c 5.0 Blood Sugar F 78 Blood Sugar pp 82 |
| 4 | 25/8/2018 | 20 | M | KCO type 1 diabetes for 1 year | HO extreme weight loss and polyuria, erectile dysfunction, Weight 37 Kg | Hba1c 14 Blood Sugar F 292 Blood Sugar pp 358 C peptide 0.1 Anti-Gad antibody 5.47 | 55 | nil | Weight gain of 13 kg in 1-year, Improved energy, improvement in erectile dysfunction | 25 | 25 | 25 | 25 | NA | Hba1c 7.8 Blood Sugar F 201 Blood Sugar pp 213 C peptide 0.3 | Hba1c 7.5 Blood Sugar F 193 Blood Sugar pp 203 C peptide 0.42 | Hba1c 7.3 Blood Sugar F 186 Blood Sugar pp 201 | Hba1c 7.4 Blood Sugar F 176 Blood Sugar pp 198 | NA |
| 5 | December 10, 2018 | 27 | M | KCO type 1 diabetes for 5 years | HO extreme weight loss and polyuria, Weight 68 Kg | Hba1c 11.8 Blood Sugar F 250 Blood Sugar pp 358 C peptide 0.05 Anti-Gad antibody 3.58 | 40 | Skin rash | Weight gain of 3 kg in 1-year, no polyuria | 25 | 20 | 20 | 20 | NA | Hba1c 7.5 Blood Sugar F 169 Blood Sugar pp 230 | Hba1c 6.5 Blood Sugar F 140 Blood Sugar pp 210 | Hba1c 6.8 Blood Sugar F 169 Blood Sugar pp 230 | Hba1c 7.0 Blood Sugar F 154 Blood Sugar pp 215 | NA |

**Table 1** (*continued*)

| Sr. No | Date of therapy | Age (Yr) | Sex | History | Clinical features | Investigations Before therapy | Insulin before therapy (IU) In 24 h | Side effects of therapy | Clinical Improvement1-year after therapy | Units of Insulin after therapy in 24 h | | | | | Investigations After therapy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr |
| 6 | December 11, 2018 | 21 | F | KCO type 1 diabetes for 15 years | HO weight loss and polyuria, weakness, Peripheral neuropathy, Weight 58 Kg | Hba1c 11.5 Blood Sugar F 250 Blood Sugar pp 350 C peptide 0.22 Anti-Gad antibody 5.47 | 50 | nil | Weight gain of 8 kg in 1-year, Improved energy, no polyuria | 25 | 25 | 25 | 25 | NA | C peptide 0.10 Hba1c 7.3 Blood Sugar F 150 Blood Sugar pp 220 C peptide 0.36 | C peptide 0.15 Hba1c 7.0 Blood Sugar F 130 Blood Sugar pp 190 C peptide 0.45 | Hba1c 7.3 Blood Sugar F 163 Blood Sugar pp 201 | Hba1c 7.1 Blood Sugar F 143 Blood Sugar pp 198 | NA |
| 7 | March 12, 2019 | 3.5 | M | KCO type 1 diabetes for 5 months | HO weight loss and polyuria, HO ketoacidosis, Weight 16 Kg | Hba1c 14 Blood Sugar F 355 Blood Sugar pp 550 C peptide 0.23 Anti-Gad antibody 29.77 | 10 | Mild nausea | Weight gain of 4 kg in 1-year, improved energy | 5 | 5 | 5 | 5 | NA | Hba1c 8.7 Blood Sugar F 203 Blood Sugar pp 248 C peptide 0.23 | Hba1c 8.3 Blood Sugar F 192 Blood Sugar pp 230 C peptide 0.56 Anti-Gad antibody 19.2 | Hba1c 8.1 Blood Sugar F 183 Blood Sugar pp 215 | Hba1c 8.3 Blood Sugar F 192 Blood Sugar pp 223 | NA |
| 8 | May 06, 2019 | 19 | M | KCO type 1 diabetes for 7 years | HO weight loss and polyphagia Weight 50 Kg | Hba1c 5.95 Blood Sugar F 126 Blood Sugar pp 210 C peptide 0.52 Anti-Gad antibody 5.2 | 42 | nil | Weight gain of 10 kg in 1-year, Improved energy, no polyphagia | 25 | 15 | 15 | NA | NA | Hba1c 4.8 Blood Sugar F 96 Blood Sugar pp 154 C peptide 0.55 | Hba1c 4.4 Blood Sugar F 90 Blood Sugar pp 140 C peptide 0.55 | Hba1c 4.0 Blood Sugar F 80 Blood Sugar pp 110 C peptide 0.75 | NA | NA |
| 9 | June 24, 2019 | 11 | M | KCO type 1 diabetes for 1years | HO weight loss and polyphagia Weight 38 Kg | Hba1c 9.4 Blood Sugar F 239 Blood Sugar pp 378 C peptide 0.23 Anti-Gad antibody 98 | 28 | Pain in abdomen | Weight gain of 6 kg in 1-year, Improved energy | 15 | 30 | 30 | NA | NA | Hba1c 7.4 Blood Sugar F 166 Blood Sugar pp 248 C peptide 0.22 | Hba1c 6.62 Blood Sugar F 143 Blood Sugar pp 228 C peptide 0.42 Anti-Gad antibody 55 | Hba1c 6.58 Blood Sugar F 141 Blood Sugar pp 221 | NA | NA |
| 10 | August 30, 2019 | 21 | M | KCO type 1 diabetes | HO stem cell therapy 1 year ago, Weight 50 Kg | Hba1c 7.5 Blood Sugar F 193 Blood Sugar | 25 | nil | Weight gain of 3 kg in 1-year, Improved energy | 10 | 0 | 0 | NA | NA | Hba1c 6.1 Blood Sugar F 128 | Hba1c 5.5 Blood Sugar F 111 | Hba1c 5.8 Blood Sugar F | | |

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Table 1 (*continued*)

| Sr. No | Date of therapy | Age (Yr) | Sex | History | Clinical features | Investigations Before therapy | Insulin before therapy (IU) In 24 h | Side effects of therapy | Clinical Improvement1-year after therapy | Units of Insulin after therapy in 24 h | | | | | Investigations After therapy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr |
| | | | | for 2 years | | pp 203 C peptide 0.42 | | | | | | | | | Blood Sugar pp 168 C peptide 0.35 | Blood Sugar pp 153 C peptide 0.65 | 121 Blood Sugar pp 161 | | |
| 11 | September 04, 2019 | 14 | M | KCO type 1 diabetes for 7 years | HO weight loss and polyphagia, bed wetting, Weight 32 Kg | Hba1c 10.5 Blood Sugar F 238 Blood Sugar pp 339 C peptide 0.02 Anti-Gad antibody 42.2 | 45 | Pain in abdomen | Weight gain of 5 kg in 1-year, Improved energy, no bedwetting | 45 | 25 | 25 | NA | NA | Hba1c 8.9 Blood Sugar F 201 Blood Sugar pp 231 C peptide 0.1 | Hba1c 8.5 Blood Sugar F 195 Blood Sugar pp 211 C peptide 0.3 Anti-Gad antibody 18 | Hba1c 8.4 Blood Sugar F 189 Blood Sugar pp 209 | NA | NA |
| 12 | September 06, 2019 | 25 | M | KCO type 1 diabetes for 7 years | HO weight loss and polyphagia, erectile dysfunction Weight 52 Kg | Hba1c 9.4 Blood Sugar F 205 Blood Sugar pp 278 C peptide 0.05 Anti-Gad antibody 17.5 | 50 | nil | Weight gain of 8 kg in 1-year, Improved energy, improvement in erectile dysfunction, no polyphagia | 30 | 20 | 20 | NA | NA | Hba1c 8.1 Blood Sugar F 167 Blood Sugar pp 215 C peptide 0.08 | Hba1c 7.8 Blood Sugar F 158 Blood Sugar pp 205 C peptide 0.1 | Hba1c 8.0 Blood Sugar F 178 Blood Sugar pp 215 | NA | NA |
| 13 | December 14, 2019 | 10 | M | KCO type 1 diabetes for 6 months | HO weight loss and polyuria Weight 38 Kg | Hba1c 11.4 Blood Sugar F 250 Blood Sugar pp 410 C peptide 0.15 Anti-Gad antibody 2000 | 18 | Mild Skin rash | Weight gain of 5 kg in 1-year, Improved energy, no polyuria | 10 | 20 | 20 | NA | NA | Hba1c 9.5 Blood Sugar F 226 Blood Sugar pp 221 C peptide 0.15 | Hba1c 8.9 Blood Sugar F 209 Blood Sugar pp 210 C peptide 0.35 Anti-Gad antibody 950 | Hba1c 9.1 Blood Sugar F 215 Blood Sugar pp 231 | NA | NA |
| 14 | December 23, 2019 | 38 | M | KCO type 1 diabetes for 5 years | HO weight loss and polyphagia, Weight 58 Kg | Hba1c 10.4 Blood Sugar F 252 Blood Sugar pp 358 C peptide 0.05 Anti-Gad antibody 1.3 | 50 | nil | Weight gain of 3 kg in 1-year, improved energy, no polyuria | 40 | 25 | 25 | NA | NA | Hba1c 8.8 Blood Sugar F 206 Blood Sugar pp 238 C peptide 0.8 | Hba1c 8.4 Blood Sugar F194 Blood Sugar pp 221 C peptide 0.15 | Hba1c 8.6 Blood Sugar F198 Blood Sugar pp 228 | NA | NA |
| 15 | December 28, 2019 | 29 | M | KCO type 1 diabetes for 8years | HO weight loss and polyuria, blurred vision, Weight 55 Kg | Hba1c 11.6 Blood Sugar F 286 Blood Sugar | 45 | Pain in abdomen | Weight gain of 6 kg in 1-year, improved energy, no polyuria, improved vision | | 25 | | NA | NA | Hba1c 9.1 Blood Sugar F 214 | Hba1c 8.6 Blood Sugar F 200 | Hba1c 8.5 Blood Sugar F | NA | NA |

Table 1 (*continued*)

| Sr. No | Date of therapy | Age (Yr) | Sex | History | Clinical features | Investigations Before therapy | Insulin before therapy (IU) In 24 h | Side effects of therapy | Clinical Improvement1-year after therapy | Units of Insulin after therapy in 24 h | | | | | Investigations After therapy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr |
| | | | | | | pp 368 C peptide 0.15 Anti-Gad antibody 17 | | | | | | | | | Blood Sugar pp 248 C peptide 0.15 | Blood Sugar pp 231 C peptide 0.35 | 196 Blood Sugar pp 221 | | |
| 16 | February 26, 2020 | 5 | M | KCO type 1 diabetes for 6 months | HO of diabetic ketoacidosis with coma, HO weakness and polyuria Weight 18 Kg | Hba1c 9.8 Blood Sugar F 235 Blood Sugar pp 358 C peptide 0.14 Anti-Gad antibody 2000 | 20 | Nil | Weight gain of 1 kg in 1-year, improved energy | 10 | 20 | NA | NA | NA | Hba1c 11.6 Blood Sugar F 286 Blood Sugar pp 395 C peptide 0.12 | Hba1c 10.8 Blood Sugar F 265 Blood Sugar pp 385 C peptide 0.24 Anti-Gad antibody 830 | NA | NA | NA |
| 17 | October 14, 2020 | 40 | M | KCO type 1 diabetes for 15 years | HO weight loss, lack of energy and polyphagia Weight 50 Kg | Hba1c 7.2 Blood Sugar F 128 Blood Sugar pp 174 C peptide 0.3 Anti-Gad antibody 12.67 | 38 | Mild nausea | Weight gain of 9 kg in 1-year, Improved energy, no polyphagia | 25 | 15 | NA | NA | NA | Hba1c 7.1 Blood Sugar F 157 Blood Sugar pp 158 C peptide 0.35 | Hba1c 6.2 Blood Sugar F 101 Blood Sugar pp 138 C peptide 0.65 Anti-Gad antibody 12.67 | NA | NA | NA |
| 18 | October 19, 2020 | 17 | F | KCO type 1 diabetes for 2 years | HO weight loss, lack of energy Weight 48 Kg | Hba1c 16.8 Blood Sugar F 256 Blood Sugar pp 333 C peptide 0.18 Anti-Gad antibody 7.4 | 45 | nil | Weight gain of 10 kg in 1-year, Improved energy | 25 | 25 | NA | NA | NA | Hba1c 10.9 Blood Sugar F 209 Blood Sugar pp 258 C peptide 0.18 | Hba1c 8.5 Blood Sugar F 158 Blood Sugar pp 238 C peptide 0.28 | NA | NA | NA |
| 19 | January 12, 2021 | 24 | M | KCO type 1 diabetes for 3years | HO weight loss, HO vision loss, blurred vision, Weight 58 Kg | Hba1c 12.2 Blood Sugar F 195 Blood Sugar pp 394 C peptide 0.25 Anti-Gad antibody 1.2 | 36 | nil | Weight gain of 8 kg in 6 months, improvement in vision | 18 | 0 | NA | NA | NA | Hba1c 8.8 Blood Sugar F 175 Blood Sugar pp 255 C peptide 0.46 | Hba1c 8.5 Blood Sugar F 150 Blood Sugar pp 245 C peptide 0.98 | NA | NA | NA |
| 20 | May 12, 2021 | 13 | M | KCO type 1 | HO of diabetic ketoacidosis | Hba1c 12.95 Blood Sugar F | 20 | Pain in abdomen | Weight gain of 2 kg in 6 months | 10 | NA | NA | NA | NA | Hba1c 9.3 Blood | NA | NA | NA | NA |

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**Table 1** (*continued*)

| Sr. No | Date of therapy | Age (Yr) | Sex | History | Clinical features | Investigations Before therapy | Insulin before therapy (IU) In 24 h | Side effects of therapy | Clinical Improvement1-year after therapy | Units of Insulin after therapy in 24 h | | | | | Investigations After therapy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr | 6 mt | 1 yr | 2 yr | 3 yr | 4 yr |
| | | | | diabetes for 12years | with coma, Dwarfism, inability to walk due to hip arthritis Weight 8.6 kg | 312 Blood Sugar pp 394 C peptide 0.25 Anti-Gad antibody 9.14 | | | | | | | | | Sugar F 155 Blood Sugar pp 210 C peptide 0.25 Anti-Gad antibody 9.14C peptide 0.55 | | | | |
| 21 | May 18, 2021 | 37 | M | KCO type 1 diabetes for 2 years | HO weight loss, HO vision loss, Weight 48 Kg | Hba1c 12.4 Blood Sugar F 295 Blood Sugar pp 380 C peptide 0.02 Anti-Gad antibody 9.14 | 36 | nil | Weight gain of 10 kg in 6 months | 25 | NA | NA | NA | NA | Hba1c 8.4 Blood Sugar F 195 Blood Sugar pp 210 C peptide 0.15 | NA | NA | NA | NA |

NA= Not Applicable.
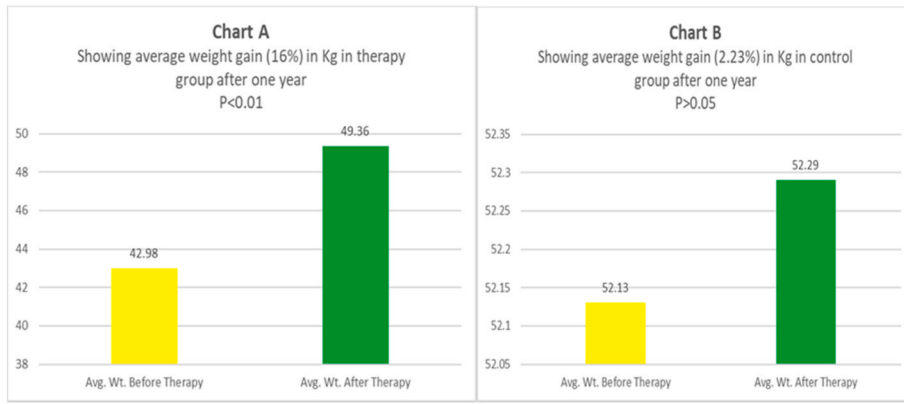
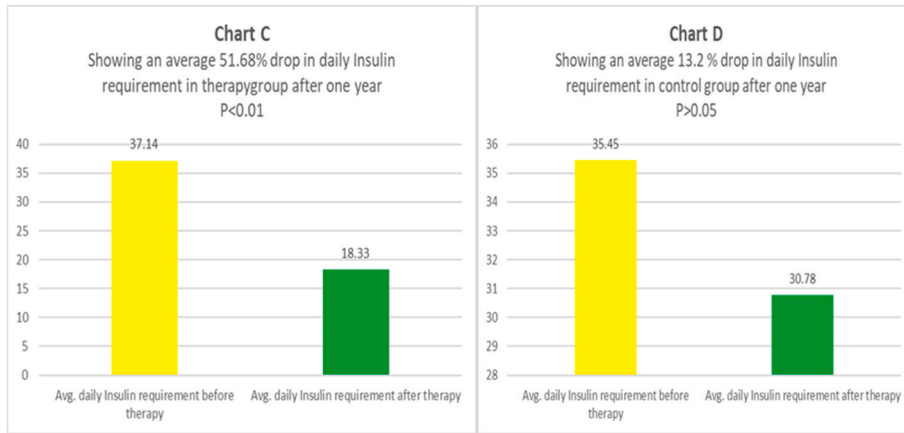**Chart A and B.** showing average and percentage weight gain in both groups.



**Chart C and D.** showing a drop in average daily Insulin requirement in therapy and control group.
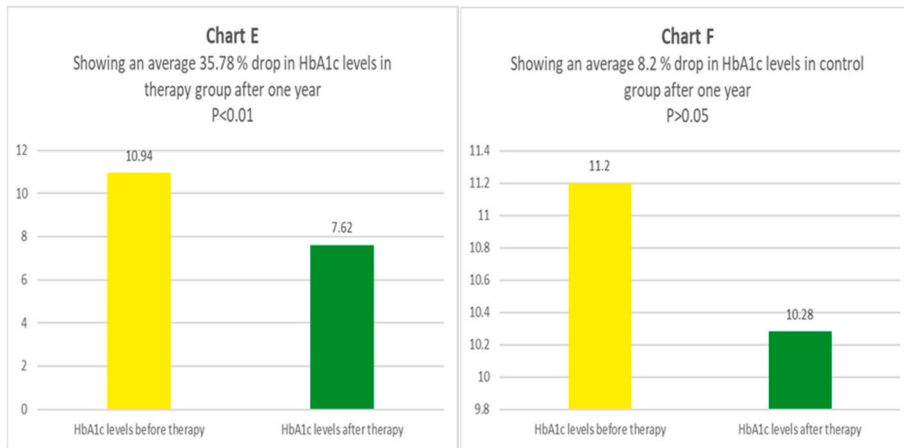


**Chart E and F.** showing average drop of HbA1c levels in therapy and control group.

them had a lower level at the end of one year (Chart N).

There were a few side effects noted after stem cell therapy, but they were largely self-limiting and minor in nature. 3 patients (14.2%) had a mild skin rash which disappeared without any treatment. 5 patients (23.8%) had post-operative pain which completely resolved with a single dose of Diclofenac Na injection as an analgesic. 2 patients (9.5%) had mild nausea which did not require any treatment.

## 18. Discussion

Adult stem cells are of 2 types [8], mesenchymal and haemopoietic stem cells. The doubling time is only 15.8 h [8]. They have potential to duplicate indefinitely and differentiate into 22 types of cells [9]. These cells typically divide for up to 6 months making them into billions of cells. These cells produce 50 types of growth factors and cytokines [11] which repair and differentiate adult tissues in an epigenetic manner. Stem cells put in a particular organ gets differentiated into cells of that

**Chart G and H.** showing average drop of fasting blood sugar levels in therapy and control group.
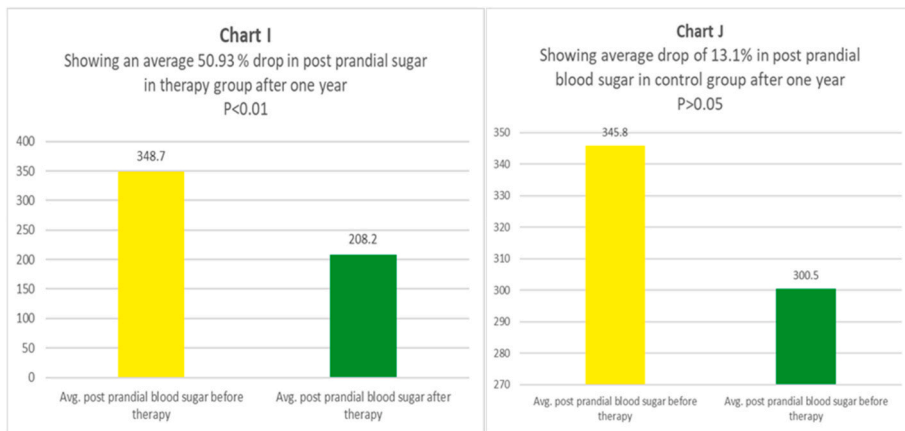


**Chart I and J.** showing average drop of post prandial blood sugar levels in therapy and control group.
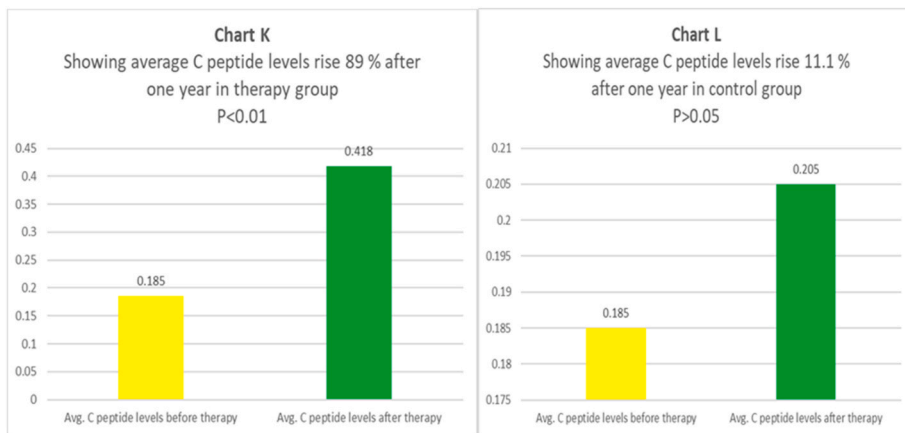


**Chart K and L.** showing average drop of C peptide levels in therapy and control group.

organ due to growth factors produced by that tissue. Mesenchymal stem cells can differentiate into tissues of all 3 lineages a phenomenon called plasticity [12–14]. Whenever a particular organ undergoes damage, stem cells in that area come fore-wards and get differentiated into specialized cells and the damage is replenished. But when the damage is extensive, the organ starts failing. By doing stem cell therapy we harvest stem cells from other healthy tissues as fat and bone marrow and put them into the diseased organ and these cells now get differentiated into specialized cells and the organ starts functioning again. In health stem

cells from fat or bone marrow can-not migrate into diseased organs, hence it is necessary to transplant them.

Autoimmune markers [15] include autoantibodies to glutamic acid decarboxylase (GAD), insulin, islet cells, islet antigens (IA2 and IA2-beta), and the zinc transporter ZnT8. Since only anti GAD antibody titer was available in my city, hence that was the autoimmune marker used in this series. C peptide levels were used instead of Insulin levels in the study for following reasons. C-peptide and insulin are released from the pancreas at the same time and in about equal amounts. Hence, a
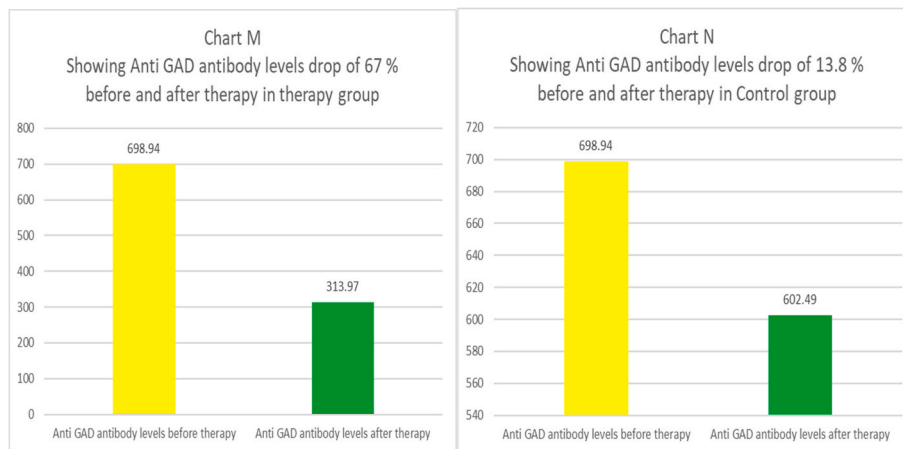
**Chart M and N.** showing average drop of Anti GAD antibody levels in therapy and control group.

C-peptide test [16] can show how much insulin your body is making. This test can be a good way to measure insulin levels because C-peptide tends to stay in the body longer than insulin. C peptide levels are constant than Insulin levels with far less fluctuations.

This Omental pouch stem cell operation (Fig. 1) is reported for the first time in the medical literature. It is based on animal studies and in vitro studies done by other researchers in the past. Stem cells were grown in hyperglycemic environment in a petri dish and after a few weeks developed into Islets like cells that started producing Insulin [17]. These Islets when implanted in diabetic rats reversed diabetes and achieved euglycemia. It is quite likely that the stem cells implanted in the Omental pouch get converted into Islet like cells and produce Insulin due to the hyperglycemic environment of the host. The stem cells acquire blood supply from the surface of Omentum just like a split skin graft which gets its blood supply from granulation tissue. It means that the Omental pouch can act as a new biological pancreas producing Insulin. But we need a separate study to prove it by taking samples of the Omental pouches after one year of therapy and study them under electron microscope to support the claims. Such studies can-not be done in humans as it will raise ethical issues and can reverse the euglycemia achieved by the patient. Following argument is the rationale of placing stem cells into the Omentum. In type 1 diabetes, many patients have auto immunity [18] and implanted Islets of Langerhans are destroyed by the autoimmunity. That makes the treatment of this disease extremely challenging. That is why, a variety of methods have been tried by the researchers in the past such as implanting the Islets into the liver, under kidney capsule, inside the liver, Omentum and into the peritoneal cavity, muscles etc. [19] Placing the stem cells in Omentum saves them from the autoimmunity as cellular immunity on Omental surface is far less than in the blood stream.

Type 1 diabetes is considered an autoimmune disorder. But there were only 6 patients (28.5%) with autoimmunity in my series. It seems that a lot of patients have a one-time damage due to viral infection [20] without auto immunity. These patients had better and long-lasting results than the autoimmunity group as there is no ongoing damage of Islets of Langerhans.

There is evidence today that bone marrow derived mesenchymal stem cells can be transdifferentiated into islet like cells which produce Insulin in Vitro [21–24]. That is the rationale of giving stem cells intravenously. Many of these cells can reach the pancreases and get differentiate into Islet like cells due to specific growth factors released by pancreas. By injecting stem cells intravenously, the autoimmunity can be reversed by the immunomodulatory function of mesenchymal stem cells [25,26].

Mesenchymal stem cells put into peritoneum of rats lead to euglycemia. The MSCs developed into Islet like cells intraperitoneally [27].

The peritoneum has only 10% cellular immunity compared to blood. Above is the rationale of placing one third isolated stem cells into the peritoneum. We already know that stem cells grow till they have 90% confluence levels. It means, stem cells will grow for much longer time in a large space. Peritoneum has a large space; hence stem cells can grow there for a very long time. Since peritoneal surface has far little immunity, the stem cells grow rapidly and for a longer time as there is little immune response against the growth of stem cells. Till the stem cells grow, they produce variety of growth factors and cytokines which are absorbed into blood, and they rejuvenate host tissues including existing Islets of Langerhans.

The therapy group had substantially good results compared to the control group (Table 1). Blood sugar fasting and post prandial, Anti Gad antibody titer, Glycosylated Hb and C peptide levels, patient's weight, and total daily Insulin requirement before and after therapy were the variables to be compared. The difference of above variables was calculated before and after therapy at the end of one year and came statistically highly significant. The therapy was partially successful in reversing auto immunity. Best results were obtained in children without auto immunity. Patients with auto immunity had relatively poor results.

Only one patient repeated the therapy after one year. Stem cells were implanted in peritoneum and blood. He had further 25–30% improvement in the variables compared. Although one patient is not statistically significant, and we need a series with a larger number of patients repeating the therapy and its results. At this stage we can hope that more patients can achieve euglycemia and Insulin independence by repeating the therapy multiple times with a gap of one year.

The study holds a great promise for future research based on above findings. Firstly, it creates hope for a dreadful disease like Type 1 diabetes patients. The allogenic cadaveric Islet cells can be transplanted into an Omental pouch instead of liver. As I have already stated, the Omental surface is best for neo angiogenesis. Hence, the newly transplanted Islets can get vascularized well in the Omental pouch. The Omental pouch surface has far little immunity compared to the blood. Hence, chances of destruction by auto immunity will be far less and the Islets may survive far longer. This study has reported partial reversal of auto immunity in Type 1 diabetes. It's a ray of hope for Type 1 diabetes patients. We need a study specially designed for reversal of auto immunity with large number of patients. The study also reports that only 6 patients (28.5%) out of 21 had auto immunity with significantly raised Anti Gad antibody levels. It supports the alternative hypothesis for type 1 diabetes which states that the disease is due to a one-time viral damage rather than due to auto immunity. If that is true, then regenerating the existing Islets of Langerhans or transplanting new ones makes a sense.

## 19. Conclusions

Autologous Stem cell therapy for type 1 diabetes with transplantation of stem cells into the Omental pouch, peritoneum, and blood was safe, and effective for the long term for the treatment of Type 1 diabetes. It also reversed auto immunity partially. We need a greater number of cases and a longer follow up to make it better. The therapy creates a lot of hope for Type 1 diabetes patients as it can be easily repeated any number of times.

### Ethical approval

Ethical committee clearance was taken from District IMA Institutional ethical committee and copy attached.

### Funding source

The study was self-funded by Dr. Sagar Jawale

### Author contribution

Dr. Sagar Jawale is the sole author.

### Registration of research studies

Name of the registry: Mendeley Data.
Unique Identifying number or registration ID: 10.17632/ 2tft8s67dw.2.
Hyperlink to your specific registration (must be publicly accessible and will be checked): https://data.mendeley.com/drafts/2tft8s67dw.

### Guarantor

Dr. Ravindra Vora, senior paediatric surgeon, India who is aware of my research Email address: voraravindra@gmail.com.

### Consent

Special informed consent was taken from all patients and attached.

### Provenance and peer review

Not commissioned, externally peer reviewed.

### Declaration of competing interest

I, the only author Dr. Sagar Jawale declare that there is no conflict of interest.

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