Bariatric Surgery is Associated with Decreased Calcineurin Inhibitor Time in Therapeutic Range after Heart Transplantation

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BACKGROUND

- Obesity increases the risk for heart failure and can lead to worse outcomes after orthotopic heart transplant (OHT).
- Severe obesity is a relative contraindication to OHT at many centers due to higher morbidity and mortality after transplant.
- Bariatric surgery (BSg) is an effective conduit to OHT eligibility, but little is known on how BSg alters the absorption and pharmacokinetics of required immunosuppressive therapy.
- Calcineurin inhibitors (CNIs) have narrow therapeutic windows and absorption may be affected by the anatomical changes from BSg.
- CNI levels fluctuate and can result in significant intra- and inter-patient variability.
- Studies have shown that high variability in CNI levels predicts poor clinical and patient outcomes, including increased risk for solid organ rejection.

OBJECTIVE

- The purpose of this study was to determine if bariatric surgery is associated with greater CNI level variability in OHT recipients.

METHODS

- Medical records were reviewed from OHT recipients between 1/2018-4/2019.
- Patients with a history of BSg prior to OHT (BSg+OHT) were compared to patients without a prior history of BSg (OHT).
- Tacrolimus and cyclosporine trough levels, cardiac biopsies, and LVEF were collected for the first 6 months post-OHT.

Table 1. Displays intervals at which data was collected for this study.

Weeks	1	2	3	4	6	8	12	16	20	24
CNI levels	x	x	x	x	x	x	x	x	x	x
Cardiac biopsy	x	x	x	x	x	x	x	x	x	x
LVEF (%)	x									x

- Measures of CNI variability:
  1. **Time in therapeutic range (TTR)**
     - Calculated as the percentage of levels in therapeutic range
  2. **Rosendaal linear interpolation method (Rosendaal TTR)**
     - Accounts for the frequency of CNI troughs and the actual levels and assumes a linear relationship between consecutive levels
  3. **Coefficient of variation (CV)**
     - Calculated as standard deviation divided by the mean multiplied by 100

RESULTS

1. **Clinical characteristics of BSg+OHT patients were similar to OHT patients.**

Table 2. Clinical characteristics for Orthotopic Heart Transplant (OHT) Patients with and without a prior history of Bariatric Surgery

	OHT with prior Bariatric Surgery† (N=4)	OHT without prior Bariatric Surgery (N=54)
Clinical Characteristics		
Age (years)	53 ± 13	57 ± 10
Female Gender	4 (100%)	13 (24%)
BMI (kg/m^2)	31.4 ± 4.5	28.1 ± 4.5
Baseline LVEF 1 week post-OHT (%)	68 ± 3	67 ± 7
LVEF 6 months post-OHT (%)	62 ± 4	61 ± 7
Patients with at least one episode of 1R/2 rejection by biopsy	3 (75%)	27 (50%)
Patients with at least one episode of 2R/3a rejection or more greater severity by biopsy	1 (25%)	11 (20%)
Cyclosporine used as the post-OHT CNI	1 (25%)	5 (9%)
Tacrolimus used as the post-OHT CNI	3 (75%)	49 (91%)

†Indicates 3 patients with prior Roux-En-Y surgery and 1 patient with prior Gastric Sleeve surgery.

2. **CNI variability analysis by TTR, Rosendaal-TTR, and CV:**

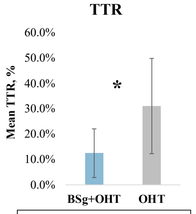

Figure 1. CNI levels were significantly less likely to be within therapeutic range among BSg+OHT vs. OHT patients (12.5% vs 31.1%, p=0.04).

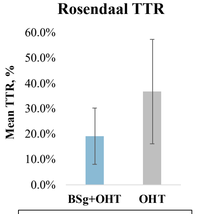

Figure 2. CNI levels were less likely to be within therapeutic range among BSg+OHT vs. OHT patients as calculated by the Rosendaal TTR method, although the results did not reach statistical significance (19.2% vs 38.8%, p=0.1).

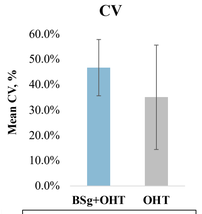

Figure 3. The coefficient of variation was larger among BSg+OHT vs. OHT patients suggesting greater CNI variability although statistical significance was not reached (46.7% vs 35%, p=0.06).

3. **Greater CNI TTR was associated with fewer episodes of cellular rejection, r = 0.31, p=0.025.**

4. **LVEF measured by echocardiogram at 1 and 24 weeks did not correlate with CNI variability.**

DISCUSSION

- The main finding of this study was CNI TTR was lower in OHT patients with a prior history of BSg.
- A trend for greater variability in CNI levels was also noted in BSg+OHT patients using two separate measures of variability: Rosendaal TTR and CV.
- We hypothesize that anatomical alterations in absorption after BSg account for this greater CNI variability.
- We also found that lower CNI TTR was correlated with higher rates of rejection.
- Previous studies have shown that greater CNI variability is associated with cellular rejection and graft failure in heart, lung, intestine, and kidney transplant recipients.
- A change in LVEF at 1 and 24 weeks was not observed in this study presumably due to early treatment of rejection once identified on cardiac biopsy.
- The main limitation of this study was the small sample size of patients with a history of BSg.

CONCLUSIONS

- BSg patients may warrant additional monitoring and adjustment of CNI levels in the early post-OHT period.
- Episodes of rejection and overall graft function were similar for BSg+OHT patients suggesting that a history of BSg should not be a contraindication to transplant.
- Larger studies are needed to determine long-term outcomes post-OHT in the BSg population.

DISCLOSURES

- There are no conflicts of interest to disclose.

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