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GLYCEMIC CONTROL BY A GLUCOSE MANAGEMENT SERVICE AND INFECTION RATES FOLLOWING LIVER TRANSPLANTATION

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Abstract

Objective—Intensive glycemic control with a dedicated glucose management service (GMS) has been used to manage hyperglycemic inpatients. We present an analysis of glycemic control before and after introduction of a GMS and outcomes within one year after liver transplantation (LT).

Methods—A retrospective review of patients undergoing LT who were treated with insulin infusions post-LT, before and after introduction of a GMS. Outcome measures within one year post-LT included rejection, infection, prolonged ventilation, and graft survival. A multiple logistic regression was used to examine the relationship between GMS use and outcomes.

Results—73 (35 GMS, 38 non-GMS) recipients were included. The mean perioperative blood glucose in the GMS group was lower than non-GMS group: unadjusted by 31.1 mg/dL (p=0.001) and adjusted for pre-insulin drip glucose, age, gender, MELD-score (Model for End Stage Liver Disease), type of transplant by 23.4 mg/dL (p=0.020). There were 27 rejection episodes, 48 infections, 26 episodes of prolonged ventilation, and 64 with graft survival at one year. Infection rate in the GMS group was lower than for non-GMS group: unadjusted OR=0.28 (p=0.015), when adjusted for pre-drip glucose, pre-transplant glucose, age, gender, MELD score, type of transplant and diabetes status prior to transplantation OR=0.24 (95% CI, [0.06, 0.97], p=0.045). There were no significant associations between GMS group and rejection rates, prolonged ventilation, or graft survival.

Conclusions—In this study of LT patients, a GMS was associated with improved glycemic control and reduced postoperative infections. Further studies investigating effects of strict glycemic control after LT are warranted.

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There are no other conflicts of interest to report.

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Intensive glucose control with use of an insulin drip infusion has been shown to improve patient outcomes in the critical care setting (1). In the last ten years, dedicated protocols and inpatient glycemic management services have been established to enable improved glycemic control. At Northwestern Memorial Hospital the institution of a Glucose Management Service (GMS), a group of dedicated nurse practitioners supervised by an endocrinology attending physician, has resulted in substantial improvements in glycemic control on surgical inpatient services in a cost effective manner (2).

Peri- and post-operative hyperglycemia in the kidney transplant population has been linked to higher rates of graft rejection and infection in a small number of studies (3, 4). We have previously shown that hyperglycemia following liver transplant also is associated with increased risk of allograft rejection (5). The effects of glucose control by a dedicated GMS in the transplant population on long-term outcomes have not been reported. The aim of this study was to compare glycemic control before and after introduction of a GMS and outcomes within one year after liver transplantation (LT).

Research Design and Methods

This study was a subgroup analysis of our previous study examining hyperglycemia in all patients following liver or liver-kidney transplantation at a single, tertiary care transplant center from February 2002 to December 2004; a more detailed explanation of methods can be found in the original study (5). This subgroup analysis was a retrospective chart review of patients who were treated with an insulin drip post-LT before (2/02-3/04) and after (3/04-12/04) the introduction of a GMS. Initial inclusion criteria included all liver and liver-kidney recipients who were treated with insulin drip infusions at any time during the post-operative period. Exclusion criteria included those who were not treated with insulin drip infusions postoperatively, had previous solid organ transplantation, had other invasive surgeries at the time of transplant, had incomplete medical records, and/or those with medical records at other institutions. Institutional Review Board approval for the study was obtained prior to data collection.

Data were collected from the inpatient medical records and outpatient transplant database. The pre-transplant period was defined as the three months prior to surgery and the peri-transplant period was defined as day of transplant to day of 1st discharge postoperatively. The post-transplant period was defined as the time of transplant to 12 months following transplant. Glucose measurements were reviewed and recorded from the pre- and peri-transplant periods. Pre-transplant variables included age, sex, MELD score (Model for End-stage Liver Disease score - a scoring system to evaluate liver disease severity) (6), average glucose levels for the 3 months prior to transplant (pre-transplant glucose status), and previous diagnosis of diabetes. Diabetic status prior to transplant was defined as a known diagnosis of diabetes recorded in the medical record, treatment with a diabetic medication, a random blood glucose level of > 200 mg/dl, or two fasting glucose levels greater than 126 mg/dl. All glucose measurements, including fasting, random, serum and point of care testing, were averaged and recorded during the pre-transplant period to evaluate pre-transplant glucose status in both diabetic and non-diabetic patients. All inpatient glucose measurements, including insulin drip and non-insulin drip glucose levels, fasting, random, serum and point of care testing, were averaged and recorded from the peri-transplant period. Glucose measurements from the time period on the insulin drip were then separately averaged and recorded. The glucose level prior to initiating the insulin drip was also recorded.

The primary outcome of interest was peri-operative blood glucose levels. Secondary outcomes were episodes of graft rejection, infection, re-hospitalization, prolonged

ventilation, and graft survival at any time following transplant up to 1 year (post-transplant period). Prolonged ventilation was defined as greater than 48 hours on a ventilator. Rejection was defined as clinical and biochemical signs followed by treatment and resolution; a biopsy was not always required for this diagnosis (5). Infection was defined as clinical signs (fever, leukocytosis, sepsis, or wound infection) and treatment with antibiotics/fungals/virals, and/or culture proven infections. Hypoglycemic events were also recorded during the peri-transplant period, defined as a glucose level less than 60 mg/dl.

The independent variable of primary interest was GMS group status. Patient characteristics were compared between patients who had glucose levels managed by the GMS and those whose glucose levels were managed by the primary transplant team (non-GMS group). No adjustments were made for multiple comparisons. The group differences in continuous and binary variables were assessed using t-test and chi-square test, respectively. Multiple linear regression analysis was used to examine the adjusted group difference in the peri-operative glucose levels. Covariates included pre-drip glucose level, pre-transplant glucose status, age, gender, type of transplant (LT or liver-kidney, LKT), MELD score and diabetes status prior to transplantation. Multiple logistic regression was used to examine the adjusted association between the secondary outcome measures and GMS group. The results from the logistic regression are summarized in terms of odds ratios and the corresponding 95% confidence intervals (CI). A $p< 0.05$ was regarded as statistically significant.

Results

Patients undergoing LT from 2/02-12/04 were examined (144 patients). Those who were treated with insulin drips post-LT before (2/02-3/04) and after (3/04-12/04) introduction of the GMS were compared for purposes of this study. In this subgroup, 73 (35 GMS, 38 non-GMS) recipients met inclusion and exclusion criteria, had a mean age 55.8 ± 9.7 years, were 66% male and 34% female, had a mean MELD score 21.1 ± 9.7, and 55 had LT alone with 18 having liver-kidney transplants. Patient characteristics by GMS group status are summarized in Table 1. There was a statistically significant difference in diabetic status in the non-GMS group vs. GMS group (24 vs. 12, p=0.019).

Average blood glucose values peri-LT and glucose levels prior to starting the insulin drip were lower in the GMS group (Table 2). Specifically, the mean peri-LT glucose level in the GMS group was lower by 31.1 mg/dl (95% CI, [12.97, 49.20], p=0.001) in the unadjusted analysis, was lower by 22.8 mg/dl (95% CI, [5.34, 40.16], p=0.013) adjusted for the pre-drip blood glucose level, and was lower by 23.4 mg/dL (95% CI, [4.18, 42.60], p=0.020) adjusted for pre-insulin drip glucose, age, gender, MELD-score, and type of transplant (Table 3). The total number of patients with one or more hypoglycemic episodes in the peritransplant period was 14 (19%), 6 of 35 patients in the GMS group and 8 of 38 in non-GMS group (p=NS).

Clinical outcomes were stratified by GMS vs. non-GMS management (Table 4). There were a total of 27 rejection episodes (37%), 48 infections (66%), 26 with (36%) prolonged ventilation, and 64 (88%) with graft survival at one year. The number of days in the Intensive Care Unit (ICU) on the first admission was greater in the non-GMS group (5.6, ±7.24) than the GMS group (3.2 days, ±4.98) (p=0.039), as was the number of hospital days on the first admission (non-GMS 11.39, ±9.00 and GMS 7.94, ±6.37) (p=NS). The infection rate in the GMS group was lower than for the non-GMS group with an unadjusted OR=0.28 (95% CI, [0.10, 0.79], p=0.015). When adjusted for pre-drip glucose, pre-transplant glucose, age, gender, MELD score, type of transplant and diabetes status prior to transplantation OR=0.24 (95% CI, [0.06, 0.97], p=0.045), and adjusted for pre-drip glucose, age, gender, MELD-score, type of transplant and average glucose OR=0.22 (95% CI, [0.06, 0.86],

p=0.029) the findings were still significant (Table 5). Infection types included bacterial, viral, and fungal etiologies along with wound and hepatobiliary infections; several patients had multiple infections and infection types at different points in time. There were no significant associations between GMS group and rejection rates, prolonged ventilation, or graft survival.

Discussion and Conclusions

The need for a systematic, cost-effective way to control inpatient hyperglycemia has been evident for some time. Recent studies have shown that computerized systems and dedicated inpatient teams and protocols have improved inpatient glucose control with fewer adverse outcomes (2,7).

In our study, glucose levels in the GMS population during the peri-operative period were lower overall. Prior to the institution of a GMS consultation group, the glucose levels were managed by the primary team, in this case, the transplant team and critical care team in the ICU. Following institution of the GMS, glucose levels were managed by trained nurse practitioners who managed all blood glucose levels in the ICU and on the inpatient floor. As discussed in detail elsewhere, such treatment involved the use of long acting basal insulin as a transition from the insulin drip for both diabetic and non-diabetic patients with subsequent prandial rapid-acting insulin (2). We did not specifically examine the exact insulin amounts diabetic and non-diabetic patients received in both groups; however, in this study glucose levels prior to the start of the insulin drip and while receiving the drip were lower in the GMS group. This may partially reflect the difference in the number of diabetic patients between the two subgroups. It is possible that prior to the institution of GMS and a standardized insulin protocol for all diabetic and non-diabetic patients, diabetic patients were more likely to be treated with an insulin drip by the primary service. GMS treated all patients who were hyperglycemic regardless of diabetic status.

Although there has been controversy over exact inpatient glucose goals in both the ICU and inpatient floors, several subgroups of patients, such as certain surgical patients, patients receiving total parental nutrition, and those treated with high dose steroids, have been shown to benefit from intensive glucose control (8, 9). At our institution, we have previously shown that surgical mortality and morbidity have been reduced in diabetic patients undergoing CT surgery through the use of combined subcutaneous and intravenous glucose strategy managed by a GMS (10). In addition post-transplant hyperglycemia in the renal and liver transplant populations has been associated with higher rejection rates (5,11). How glucose control in these patients is achieved is variable and institution dependent. However, establishment of a dedicated GMS may improve outcomes for certain subpopulations of patients. It should also be noted that the introduction of the GMS service at our institution was perceived by all members as a positive addition to the transplantation team.

In our study, infection rates for up to one year post-transplant were found to be significantly lower in the GMS population, even after adjustment for several variables. Intra-operative and post-operative hyperglycemia has previously been associated with increased risk of post-transplant infections (4,12). In our analysis rejection rates were also lower in those with in the GMS group, albeit this finding was not statistically significant, perhaps because our study was underpowered to detect such a difference.

There are several limitations to this study. Because this was a retrospective chart review, the number of glucose measurements, specifically following treatment and discontinuation of the insulin drip varied from patient to patient. The primary transplant team had no protocols for insulin adjustment or continuation of subcutaneous insulin following discontinuation of

the insulin drip. The number of glucose measurements and treatment ordered for elevated glucose levels were dependent on the primary team for those in the non-GMS group and varied greatly. Glucose measurements were a combination of point of care, serum, fasting, and non-fasting values. At that time, hemoglobin A1C levels were not routinely drawn prior to or following transplantation.

This time period for review was chosen because it was when the GMS was first implemented in the hospital. Only those treated with insulin drips during their hospitalization from that time period were reviewed. Also, there were minimal changes in surgical techniques, immunosuppression protocols, and other aspects of transplant care during the established, narrow time period. In this way, we were able to compare those with and without a GMS consult, with all other aspects of care being similar.

In our study, infection rates were lower in patients in the GMS group after adjustment for pre-drip glucose levels, age, gender, MELD score, type of transplant and average blood glucose and repeat adjustment for pre-drip glucose, pre-transplant glucose, age, gender, MELD score, type of transplant and diabetes status prior to transplantation. The reduction in post-operative infections was only partially explained by mean glucose improvement. Whether the institution of the GMS service had any additional effect on clinical outcomes is unclear. The average glucose levels were lower in the GMS population, but the variation of glucose levels may have also been a contributing factor. Other retrospective analyses from three different groups have shown glucose variability as a significant predictor of mortality for patients in the intensive care unit (13-15). Those patients treated by the GMS were more likely to receive both IV and subcutaneous long and rapid acting insulins during their stay regardless of diabetes status, possibly contributing to a decrease in glycemic variation from the ICU through inpatient floor care (2).

Currently there are no guidelines for transition of care between ICU and floor management of glucose levels or on the variability allowed throughout the entire post-surgical stay. It has been known that a dedicated GMS can improve glycemic control and we have developed methods for effecting a smooth transition from IV to subcutaneous insulin upon transfer of patients from the ICU to the floor (2,16). There is, however, limited literature linking this type of service, glycemic control, and improvement of patient outcomes (infection rates). Our data suggests an association between reduced infection rates and glucose control by the GMS but our patient populations were small and the study was a retrospective analysis. Prospective trials investigating institutional protocols and services, transitions of insulin care, and variability of blood glucose management in certain post-surgical populations are warranted.

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Table 1

Baseline characteristics of patients undergoing liver transplantation who were treated with insulin drips postoperatively

	Non-GMS† Group (N=38)	GMS Group (N=35)	p value
Age	57 (± 8.8)	54.5 (±10.6)	0.273
Gender (% F)	12 (31.6%)	13 (37.1%)	0.617
MELD* score	22.8 (± 9.8)	19.3 (± 9.6)	0.130
Liver-Kidney Transplant	7 (18.4%)	11 (31.4%)	0.202
Known Diabetes	24 (63%)	12 (34%)	0.019

*MELD – Model of End Stage Liver Disease;

†GMS – Glucose Management Service

Table 2

Average in hospital glucose levels (mg/dl) prior to being treated on insulin drip, during the time treated with an insulin drip, and all glucose levels immediately following Liver Transplantation (drip and non-drip during the peri-transplant period).

	Non-GMS* Group (N=38)	GMS Group (N=35)
Average Glucose (pre-drip)	304.1 (± 89.8)	257.0 (± 84.2)
Average Glucose (on insulin drip)	182.94 (± 51.71)	165.98 (± 43.31)
Average Glucose (peri-Liver Transplantation)	189.0 (± 45.0)	157.9 (± 32.3)

*GMS – Glucose Management Service

Table 3

Differences in peri-operative glucose levels between patients treated by GMS* compared to those not treated by the GMS service using multivariable regression analysis

	Glucose Difference (mg/dl)	95% CI	P Value
Unadjusted	-31.1	[12.97, 49.20]	p= 0.001
Adjusted for Pre-drip Glucose level	-22.8	[5.34, 40.16]	p= 0.013
Adjusted for Pre-drip Glucose and Pre-transplant Glucose (avg over 3 months)	-13.92	[-3.84, 31.67]	p= 0.129
Adjusted for Pre-drip Glucose, Age, Gender, MELD† Score, Type of transplant	-23.4	[4.18, 42.60]	p= 0.020
Adjusted for Pre-drip Glucose, Pre-transplant glucose, Age, Gender, MELD score, Type of transplant and Diabetes status prior to transplantation	-12.22	[-7.37, 31.82]	p= 0.226

*GMS – Glucose Management Service;

†MELD – Model of End Stage Liver Disease

Table 4

Post-Transplant Clinical Outcomes

	Non GMS* Service % N=38	GMS Service % N=35	p value
Rejection	44.7% N=17	28.6% N=10	0.156
Re-Hospitalization	63.2% N=24	71.4% N=25	0.453
Infection	78.9% N=30	51.4% N=18	0.015
Graft Survival	81.6% N= 31	94.3% N=33	0.117
Prolonged Ventilation	39.5% N=15	31.4% N=11	0.474

*GMS – Glucose Management Service

Table 5

Post-transplant Infection Rates

	GMS† Group vs. Non GMS Group	95% CI	p value
Unadjusted	OR= 0.28	[0.10, 0.79]	p= 0.015
Adjusted for Pre-drip Glucose	OR= 0.26	[0.09, 0.77]	p= 0.015
Adjusted for Pre-drip Glucose, Pre-transplant glucose, Age, Gender, MELD* score, Type of transplant and Diabetes status prior to transplantation	OR= 0.24	[0.06, 0.97]	p= 0.045
Adjusted for Pre-drip Glucose, Age, Gender, MELD score, Type of transplant and Average glucose	OR= 0.22	[0.06, 0.86]	p= 0.029

*MELD – Model of End Stage Liver Disease;

†GMS – Glucose Management Service