

Liraglutide is a Perioperative Therapeutic Option for Patients with Type 2 Diabetes that Undergo Elective Surgery

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Abstract

Diabetic patients that perform limited amounts of exercise during perioperative periods tend to gain weight, and their glycemic control frequently deteriorates. However, temporary insulin therapy is associated with a risk of hypoglycemia. To investigate the efficacy and safety of preoperative liraglutide therapy, we performed a retrospective analysis of the cases of Japanese type 2 diabetes mellitus (T2DM) patients that underwent elective surgery.

Liraglutide therapy was initiated in patients with T2DM prior to elective surgery. Regular insulin was also administered in cases in which hyperglycemia (plasma glucose > 200mg/dl) was detected during operations. The glycemic level, the insulin dose during the perioperative period, body mass index (BMI), and perioperative complications were analyzed.

Seventy-three patients with T2DM (male/female: 40/33, age: 69.5±11.0, glycated hemoglobin (HbA1c): 7.8 ±1.3, BMI: 26.6±4.1) were administered liraglutide therapy before undergoing elective surgery; i.e., orthopedic operations (40 cases); cardiac catheterization for ischemic heart disease(12 cases); ophthalmological operations, including procedures for cataracts (13 cases); prostatectomy (2 cases); mastectomy (1 case); unilateral nephrectomy (1 case); total hysterectomy (1 case); total bladder extirpation (1 case); plastic surgery (1 case); and angioplasty for a hemodialysis shunt (1 case).

The preoperative administration of liraglutide therapy resulted in reductions in body weight (mean: -3.1 ± 2.0 kg) and good glycemic control throughout the perioperative period. Additional regular insulin was only required in 11 patients, who were prescribed ≤ 10 units each. No hypoglycemic episodes, delayed wound healing, or other complications were observed. The patients' HbA1c levels remained within the normal range (mean: 6.8±0.8%) at 6 postoperative months. Liraglutide represents an effective therapeutic option for safely achieving good glycemic control in perioperative patients with T2DM, especially those who have a limited exercise ability or are at risk of hypoglycemia.

Introduction

Diabetic patients that remain in a sedentary state during the perioperative period tend to gain weight, and their glycemic control frequently deteriorates. There is substantial evidence linking hyperglycemia in surgical patients with unfavorable outcomes. On the other hand, temporary insulin therapy requires frequent monitoring of blood glucose levels and carries a risk of hypoglycemia. A recent large study into this topic (the NICE-SUGAR study) [1] suggested that intensive insulin therapy significantly increases the risk of hypoglycemia and does not have any beneficial effects on the overall mortality rate among critically ill patients.

Analogues of incretins, which are glucagon-like peptide-1 (GLP-1) receptor agonists, are widely used to treat type 2 diabetes (T2DM) since they do not tend to induce weight gain and are associated with a low risk of hypoglycemia [2]. But data about the therapeutic application of these drugs instead of insulin for perioperative glycemic control are scarce [3-5]. To investigate the efficacy and safety of the perioperative use of liraglutide therapy, a GLP-1 receptor agonist, as a non-insulin agent for achieving perioperative glycemic control, we performed a retrospective analysis of the cases of patients with T2DM who underwent elective surgery at two separate hospitals.

Methods

A retrospective analysis of a total of 86 elective surgical procedures performed on 73 patients with T2DM at two separate hospitals between October 2010 and October 2013 was carried out.

As liraglutide decreases gastrointestinal motility, cases involving gastrointestinal surgery were not included.

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Treatment protocol

Informed consent was obtained from all patients, and the liraglutide therapy was initiated after the cessation of oral antidiabetic drugs.

In cases in which hyperglycemia occurred during the perioperative period, regular insulin was added to the therapy if necessary.

The preoperative target blood glucose level ranged from 140 to 160 mg/dl (the 2-hour post-prandial blood glucose level), and during operations it ranged from 150 to 250 mg/dl. In the cases involving hyperglycemia, regular insulin was added at a dose that was appropriate to the patient's blood glucose level before each meal (Figure 1).

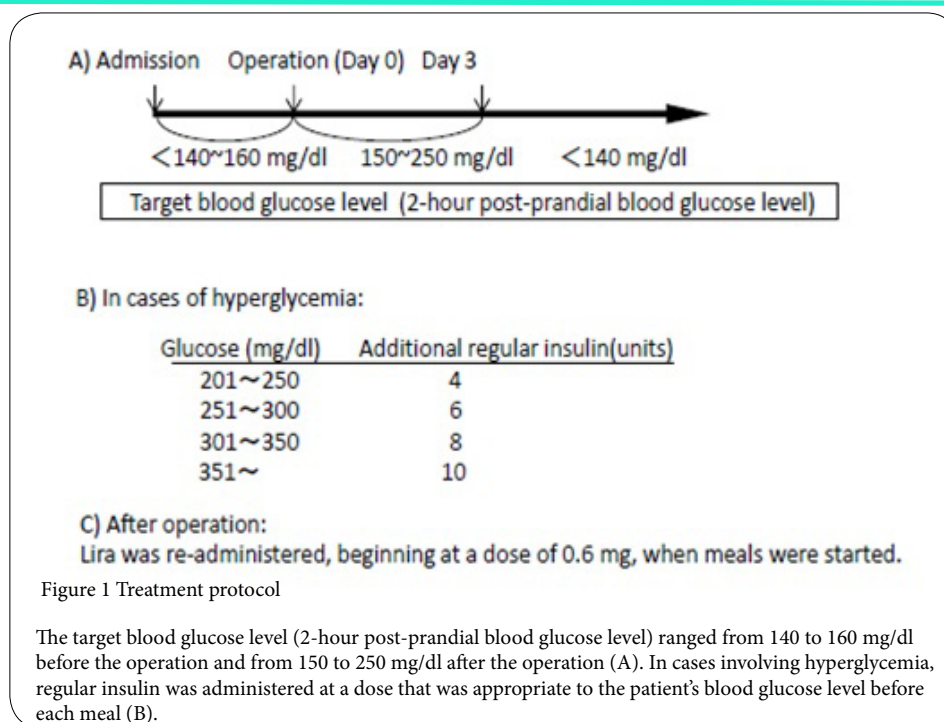
Postoperative period

Liraglutide was re-administered, beginning at a dose of 0.6 mg and increasing to the maximum dose, when meals were restarted.

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Body mass index (BMI), blood glucose levels, hypoglycemia, the insulin dose (if required), the medication administered before the liraglutide therapy, and perioperative complications were analyzed.

In the patients who underwent ophthalmological operations, no glycemic measurements were obtained on the day on which the liraglutide therapy was initiated, the day before the operation, or the day after the operation because these patients were admitted on the day of the operation and discharged the next morning. In addition, the glycemic level was not measured on the day of the operation in the patients that underwent cardiac catheterization.

Data are presented as mean \pm SD. The Student's t-test was employed for statistical analyses.

Results

Patients

Seventy-three patients (males: 40) with T2DM underwent liraglutide therapy between October 2010 and October 2013 at two clinical institutions (Table 1).

The patients' baseline characteristics were as follows: male/female, 40/33; mean age, 69.5 ± 11.0 years old; mean HbA1c level, 7.8 ± 1.3 %; mean BMI, 26.6 ± 4.1 ; mean disease duration, 11.7 ± 10.7 years.

In all cases, liraglutide therapy was initiated prior to elective surgical procedures, which included orthopedic operations (40 cases); diagnostic or therapeutic cardiac catheterization for ischemic heart disease (12 cases); ophthalmological operations, including procedures for cataracts (13 cases); prostatectomy or prostate needle biopsy for prostate cancer (2 cases); mastectomy for breast cancer (1 case); unilateral nephrectomy for renal cancer (1 case); total hysterectomy for uterine cancer (1 case); total bladder extirpation for cancer (1 case); plastic surgery (1 case); and angioplasty for a hemodialysis shunt (1 case).

In the cases in which hyperglycemia occurred during the perioperative period, regular insulin was added at a dose that was appropriate to the patient's blood glucose level before each meal (Figure 1).

One patient with osteoarthritis of the knee was administered Liraglutide therapy but their operation was subsequently cancelled as they lost weight and their pain disappeared.

Medication administered before the liraglutide therapy

Regarding the medications administered before the liraglutide therapy, 14 patients did not receive any other medications before the liraglutide therapy, 43 patients were given oral medication, 27 patients were treated with sulfonylurea and. In the latter patients, the mean dose of glimepiride was 1.3 ± 1.1 mg per day. In addition, 16 patients were administered insulin (mean dose of insulin glargine: 10.6 ± 5.0 units per day).

Glycemic control

Compared with the values recorded on admission, the use of liraglutide improved the patients' preoperative blood glucose levels (Table 2). Furthermore, their postoperative blood glucose level sneaked at 250 mg/dl.

The patients' mean glucose levels on the day on which liraglutide therapy was first administered, the day before the operation, the day of the operation, and the day after the operation were 198.0 ± 47.5 (not including the patients that underwent ophthalmological operations), 144.2 ± 26.5 (not including the patients that underwent ophthalmological operations), 126.0 ± 27.2 (not including the patients that underwent cardiac catheterization for ischemic heart disease) ($p < 0.01$), and 164.4 ± 40.0 (excluding the patients that underwent ophthalmological operations) ($p < 0.01$) mg/dl, respectively.

		Total				
Number of cases(male/female)		73(40/33)				
Number of procedures(male/female)		86(49/37)				
Age(yrs)		69.5±11.0				
NbA1c(%)		7.8±1.3				
MBI		26.6±4.1				
Disease durations(yrs)		11.7±10.7				
	Orthopedics operations	Cardiac catheterization	Ophthalmological operations	Others		
Number of cases(male/female)	40(17/23)	12(10/2)	13(9/4)	8(4/4)		
Number of procedures(male/female)	43(18/25)	19(17/2)	18(12/6)	9(5/4)		
Age	67.8±13.5	68.4±7.9	72.7±7.4	74.9±3.2		
BMI	27.2±4.0	24.0±2.4	24.4±2.8	29.0±7.6		
HbA1c(%)	7.4±1.1	8.6±1.8	8.6±1.1	7.6±0.5		
Disease duration(yrs)	11.2±10.7	14.0±12.6	Unknown	9.5±7.8		
Medications administered before Lira therapy						
None		8	4	1	1	1
OAD	Number of medications	1	5	0	1	1
		2	15	2	5	3
		3	3	2	0	0
		4	5	1	0	0
		With SU**	17	4	2	4
Insulin therapy***	4	3	6	3		
Fasting CPI	1.4±0.6	1.3±0.1	NM	NM		
uCPR(μ/day)	94.0±60.6	77.7	NM	NM		

Table 1 Case profiles *: disease (cases): prostate cancer(2), breast cancer(1), renal cancer(1), uterus cancer(1), bladder cancer(1), plastic surgery(1), dialysis shunt(1), **: SU (mg per day) : glimepirid 1.3±1.1, glibenclamide 5.6±3.1. ***: insulin dose (unit per day) 10.6±5.0.

	Orthopedic operations	Cardiac catheterization	Ophthalmological Operations	Others
Regular insulin(4)	12	None	2	2
Regular insulin(Units/day)	6.4±4.5	0	7±1.4	4±0

Table 2: Insulin doses required on the day of the operation.

Additional regular insulin was only required on the day of the operation in 16 patients, and 6.3±4.1 units of regular insulin were administered in these cases.

Insulin doses prescribed during the perioperative period

Additional regular insulin was only required on the day of the operation in 16 patients, and 6.3 ± 4.1 units of regular insulin were administered in these cases (Figure 2).

Body weight and BMI

The body weights of most of the patients decreased after the preoperative liraglutide therapy until the day before the operation (mean: -3.1 ± 2.0 kg), and the mean BMI change of the patients that received preoperative liraglutide therapy (except one orthopedic patient) was -1.2 ± 1.3 (Figure 5).

The body weight loss induced by liraglutide therapy facilitated efficient rehabilitation.

Hypoglycemic episodes and adverse events

No adverse incidents such as hypoglycemic episodes, delayed wound

healing, or other complications were observed in any of the cases.

Others

On the day of the operation, the patients' mean systolic blood pressure was 123.7 ± 12.8 mmHg. The patients' HbA1c levels remained within the normal range (6.8 ± 0.8%) at 6 postoperative months.

Discussion

Insulin is the gold standard treatment for hyperglycemia in surgical patients. However, in the perioperative period, counter-regulatory hormones, such as catecholamines, glucagon, cortisol, and growth hormones, are released as a response to stress, which causes insulin resistance and hepatic glucose production and results in hyperglycemia [6]. In addition, insulin therapy requires frequent glucose measurements and dose adjustment by well-trained medical providers, especially during the perioperative period, when patients' caloric intakes vary. The present results suggest that liraglutide can be

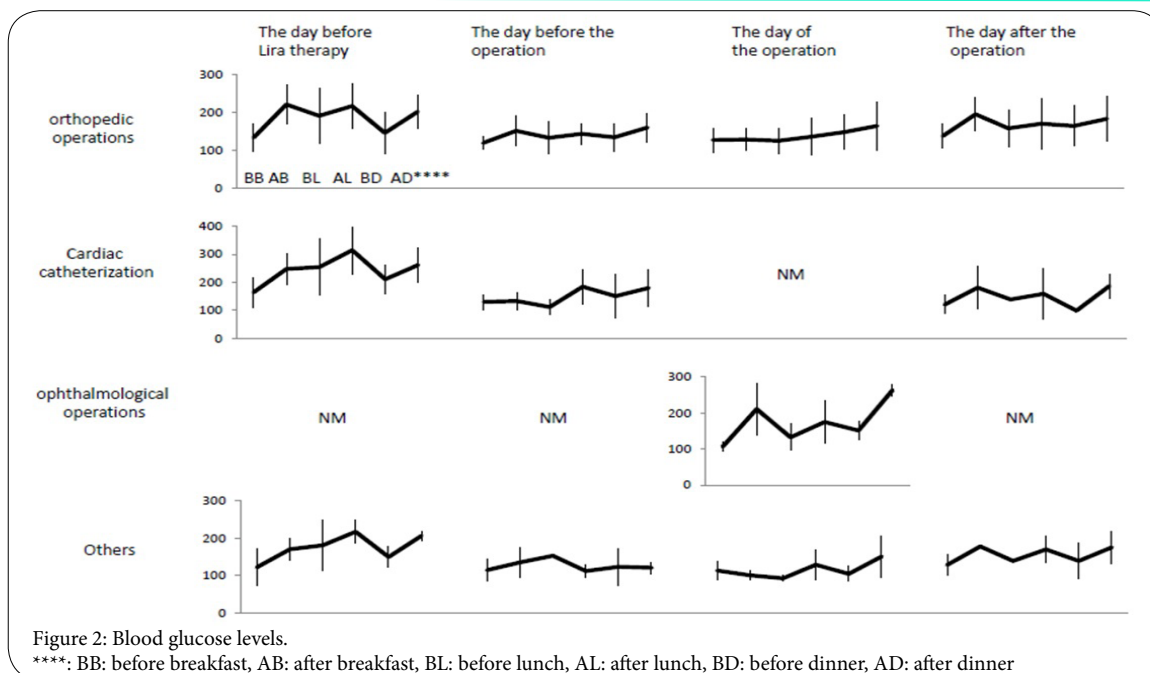


Figure 2: Blood glucose levels.
 ****: BB: before breakfast, AB: after breakfast, BL: before lunch, AL: after lunch, BD: before dinner, AD: after dinner

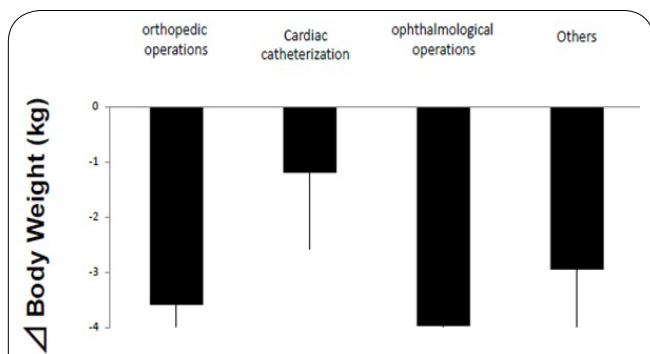


Figure 5: The changes in body weight.
 The body weights of the patients decreased during liraglutide therapy until the day before the operation (mean \pm SD).

perioperatively administered to selected stable diabetic patients who are expected to consume meals at regular intervals without dose adjustment instead of insulin.

Hyperglucagonemia, which stimulates hepatic glucose production and causes severe insulin resistance in peripheral tissues [7], sometimes occurs in the postoperative period. Since liraglutide contributes to inhibiting glucagon secretion in the liver and improves hyperglycemia, we consider that it might be useful for reducing hyperglucagonemia in the postoperative period.

There are two further reasons why liraglutide, a GLP-1 agonist, is recommended as a therapeutic option for achieving glycemic control in elective perioperative patients. The first is that liraglutide is associated with a minimal risk of hypoglycemia [8]. Hypoglycemia is a serious complication of insulin therapy that is associated with a minimal risk of hypoglycemia [8]. Hypoglycemia is a serious complication of insulin therapy that is associated with many adverse cardiovascular events and has a negative impact on the mortality rate of hospitalized patients. In contrast, it has been reported that liraglutide has some beneficial effects on the cardiovascular system. Not only does it carry a low risk of hypoglycemia, but it also improves endothelial function,

myocyte viability, and coronary artery vasodilation, etc. Considering these effects, liraglutide is useful especially in patients who are at high risk of ischemic heart disease [9,10].

The second point is that liraglutide inhibits weight increases [11,12]. In the perioperative period, diabetic patients, especially those with limited exercise ability, e.g., patients undergoing orthopedic operations, tend to gain weight, and their glycemic control frequently deteriorates. As liraglutide lowers gastric emptying, which attenuates postprandial glycemic variations, it also decreases appetite [13]. The avoidance of weight gain before surgery leads to the maintenance of good glycemic control, even in the postoperative period. In addition, weight reductions would be expected to directly improve orthopedic conditions.

Clinicians should be aware of the following points: 1) As liraglutide is only available for patients whose β -cells secrete sufficient amounts of insulin, patients who are already dependent on insulin therapy or who have diabetic ketoacidosis or pancreatitis should be excluded from such treatment. 2) Moreover, as liraglutide decreases gastrointestinal motility, the use of liraglutide in patients that are scheduled to undergo gastrointestinal surgery should be avoided. 3) In cases in which postoperative hyperglycemia occurs, which is considered to be induced by overactive stress hormones, additional regular insulin should be considered to prevent postoperative complications, such as ketoacidosis, infection, and delayed wound healing occurring.

The limitations of the present study include the fact that it was conducted in a retrospective non-randomized manner, and so our findings need to be validated in a prospective, placebo-controlled study.

Conclusion

Liraglutide represents an effective therapeutic option for safely achieving good glycemic control in perioperative patients with T2DM, especially those who have a limited exercise ability who are at risk of hypoglycemia.

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