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Research Article

CASE SERIES - INSULIN INFUSION THERAPY IS EFFECTIVE IN HYPERTRIGLYCERIDEMIA-INDUCED ACUTE PANCREATITIS

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ABSTRACT

Objective: Hypertriglyceridemia (HTG) is responsible for up to 10% of all acute pancreatitis (AP) cases. The objective of this study is to present the effects of insulin infusion therapy in HTG-induced AP.

Methods: We had 11 patients with AP and high triglycerides between June 2020 and January 2021 admitted to Bharati Vidyapeeth Medical College and Hospital in Pune, Maharashtra, India. Following laboratory and imaging evaluations, all patients were treated with insulin infusions and supportive care. Following the achievement of triglyceride (TG) level <1000 mg/dL, patients were given Fenofibrate 160 mg OD and Saroglitazar 4 mg OD. We observed their recuperation during the treatment duration.

Results: Our study included 11 AP patients ranging from 18 to 50 years of age, five men and six females. This group included diverse patient population obese, non-obese, diabetic, and non-diabetic patients. TG values ranged from 2200 to 8000 mg/dL, with a mean of 5345.4±1203.8 mg/dL. There were nine patients with moderate pancreatitis, two with mild pancreatitis, and none with severe pancreatitis. Insulin infusions in the range of 302–1008U were required for 2–4 days. TG dropped 17–41% on the 2nd day of insulin infusion and 59–75% on the 3rd day. In all patients, TG levels fell below 1000 mg/dL after 4 days of insulin infusion, and then they were treated with oral anti-lipid medications. Hospital stay ranged from 9 to 25 days, with a 100% recovery rate.

Conclusion: Insulin infusion can be used to treat HTG-induced AP with minimal risk of complications.

Keywords: Hypertriglyceridemia, Acute pancreatitis, Insulin infusion.

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INTRODUCTION

Hypertriglyceridemia-induced pancreatitis (HTIP) is a relatively uncommon but well-known clinical disease. Chylomicronemia is characterized as a TG level >1000 mg/dL, while chylomicronemia syndrome (CS) is defined as TG >1000 mg/dL plus one of the eruptive xanthomas, lipemiaretinalis, or abdominal pain/pancreatitis [1]. The most common causes of pancreatitis are biliary stones and alcohol intake; nevertheless, hypertriglyceridemia (HTG) is a rare but well-known cause of pancreatitis, accounting for up to 10% of all cases [2].

HTG is difficult to classify since it can be caused by genetic (primary) and environmental (secondary) factors. Primary severe HTG (TG 10 mmol/l) can develop as a result of an autosomal recessive, monogenic familial CS in a small percentage of people (2%), (FCS, former Type I). The majority of severe HTG cases, on the other hand, are multifactorial, the result of polygenic (mixed HTG, former Type V) determinants and secondary variables. Mild-to-moderate HTG cases (2–9.9 mmol/l TG) are also polygenic and have a complex genetic susceptibility (former Type IV, Type IIB, and Type III) [3-5].

Chylomicrons or triglycerides (TG) get digested by pancreatic lipase to release free fatty acids (FFA), which cause pancreatic capillary inflammation and thrombosis in the pancreatic capillary bed, resulting in pancreatitis [6]. The objective of this study is to present the effects of insulin infusion therapy in HTG-induced acute pancreatitis (AP).

METHODS

We described the clinical course and outcomes of 11 patients with AP and raised TG who were admitted to Bharati Vidyapeeth Deemed to Be University Medical College and Hospital in Pune, Maharashtra, between June 2020 and January 2021, and Institutional Ethics Committee approval was taken for the study.

A complete clinical history was collected, the patients reported a history of acute abdominal pain, and elevated amylase and TG levels were part of our series. There was no history of alcohol or drug use. Laboratory evaluations, such as complete blood count, renal function tests, liver function tests, international normalized ratio, amylase, lipid profile, C-reactive proteins (CRP), and serum calcium levels, were performed. Abdominal ultrasonography was performed on admission, and computed tomography (CT) with contrast enhancement was performed on the 3rd day. CT severity score and Atlanta classification were used to determine severity [7,8].

All patients were kept nil per-oral, and intravenous fluid resuscitation with normal saline and ringer lactate was started at a rate of 100–150 ml/h. Fluid resuscitation was adjusted based on urinary output, clinical condition, and vitals. In addition to fluid resuscitation, analgesics were added as needed, and insulin infusion was started at 0.1 u/kg/h. If TG levels fell by <30%, insulin doses were increased based on daily follow-up. If TG levels dropped by more than 50%, we reduced insulin infusion to avoid recurrent hypoglycemia. We checked blood sugar levels every 4 h and transfused 25% dextrose if they were less <90 g/ml or if hypoglycemic symptoms were present. Once TG were <1000 mg/dL, we started patients on oral antilipidemic drugs, saroglitazar 4 mg, and fenofibrate 160 mg, either alone or in combination depending on TG levels.

Supportive care was maintained with analgesic antilipidemic drugs, antibiotics, and anticoagulants as needed. Patients were discharged on oral anti-lipid, analgesics, and oral hypoglycemic if people with diabetes

were detected. After 15 days, all patients were followed up with a lipid profile. Following a 15-day follow-up, all patients were referred to an endocrinologist for further lipid management. Descriptive statistics were used for analyzing the results.

RESULTS

We had 11 patients ranging in the age from 18 to 50 years (mean: 32.3±5.2). There were five males and six females. Weight ranged from 51 to 70 kg (58.4±3.08 kg), with a body mass index (BMI) of 20.8–26 kg/m^2 (22.6±0.8 kg/m^2). According to the WHO obesity classification, two patients are obese, one is overweight, and the rest have a normal BMI. Four patients have recently been diagnosed with diabetes and HTG (Table 1).

The symptoms of all of the patients were the same: Acute abdominal pain, nausea, and vomiting of varying degrees of severity. On clinical examination, all reported tachycardia and moderate to severe abdominal tenderness in the epigastrium and periumbilical area. At the presentations, blood pressure was normal, and there was no fever or other complications.

Nine of the patients had microcytic hypochromic anemia (Hb-7.7–10.2 g/dL), whereas the other two had normal hemoglobin. These anemic patients had no history of hematemesis or melena, and their stool tests for occult blood were negative. Patients with hemoglobin levels <8 g/dL had blood transfusions, while the others received oral iron supplementation. Leukocytosis was more common in patients with greater CT severity scores ($p<0.05$ for). Only one patient had thrombocytosis, and the rest had platelet counts were within normal ranges. Renal parameters, and electrolytes are all within normal ranges.

Amylase and CRP levels were high, 398.9±82.5 mg/L and 73.0±15.8 mg/L, respectively. The greater the CT severity score,

Table 1: Baseline characteristics, evaluation, and outcome

S. No.	Age	Sex	Wt. in kg	BMI kg/m^2	Comorbidity	Clinical presentation	Clinical examination	BP (mm/hg)	PR per min	Hospital course	Hospital stay course (days)	Outcome	Recurrence
1	30	M	60	21.8	Newly detected DM	P, N, V	Severe tenderness at the umbilical area with mild guarding	110/80	130	Supportive care and insulin (R) inf.	18	Recovered	Yes
2	25	M	62	22.5	No	P, N, V	Moderate tenderness at umbilical area	130/84	122	Supportive care and insulin (R) inf.	12	Recovered	No
3	36	M	58	22.1	No	P, N, V	Moderate tenderness at umbilical area	122/84	118	Supportive care and insulin (R) inf.	10	Recovered	No
4	40	F	60	26	Newly detected DM	P, N, V	Severe tenderness at the umbilical area and guarding	120/86	116	Supportive care and insulin (R) inf.	16	Recovered	Yes
5	28	F	58	25.1	No	P, N, V	Moderate tenderness at umbilical area	120/90	110	Supportive care and insulin (R) inf.	12	Recovered	No
6	50	F	53	22.6	No	P, N, V	Severe tenderness at umbilical area	140/80	120	Supportive care and insulin (R) inf.	17	Recovered	Yes
7	41	M	63	20.8	No	P, N, V	Mild tenderness at umbilical area	144/80	100	Supportive care and insulin (R) inf.	10	Recovered	No
8	33	M	70	23.1	No	P, N, V	Severe tenderness at the umbilical area and guarding	130/86	123	Supportive care and insulin (R) inf.	25	Recovered	No
9	34	F	51	21.5	Newly detected DM	P, N, V	Mild tenderness at umbilical area	126/74	100	Supportive care and insulin (R) inf.	9	Recovered	No
10	18	F	55	22.3	Newly detected DM	P, N, V	Moderate tenderness at umbilical area	110/80	128	Supportive care and insulin (R) inf.	12	Recovered	No
11	21	F	53	21.8	No	P, N, V	Moderate tenderness at umbilical area	140/80	116	Supportive care and insulin (R) inf.	14	Recovered	No

BMI: Body mass index, BP: Blood pressure, PR: Pulse rate, P: Pain, N: Nausea, V: Vomiting, DM: Diabetes mellitus, Insulin (R) R: Regular insulin, Inf.: Infusion

the greater was the CRP and amylase levels, and the greater was the leukocytosis ($p<0.05$). Diabetes mellitus was diagnosed for the first time in four patients (mean blood sugar 367.75±59.6 g/dL) (Table 2).

The liver function and renal function were normal in all patients throughout the course. Total cholesterol was 64.6±3.3 mg/dL, TG were 5345.4±1203.8 mg/dL, low density lipoproteins were 63.4±3.62 mg/dL, and high density lipoproteins were 36.8±2.2 mg/dL in a fasting lipid profile. TG levels ranged from 2200 to 8000 mg/dL. The higher the TG value, the more severe was the pancreatitis with a high CT severity index and CRP ($p<0.05$). Higher TG patients required more hospitalization due to severe pancreatitis and TG normalization ($p<0.05$).

Four patients had necrotizing pancreatitis with fluid collection on contrast-enhanced CT, whereas the other five had peri-pancreatic fluid accumulation without necrosis. In two cases, the pancreas was edematous, but there was no fluid accumulation. There was no transient or long-term organ failure. The CT severity score ranged from 2 to 6 (4.36±0.8). According to the Atlanta classification, nine patients had moderate pancreatitis, two had mild pancreatitis, and none had severe pancreatitis (Table 3).

Infusion of insulin was necessary for 2–4 days, with total insulin in the range of 302–1008U (539.5±134.8U). More the TG levels insulin requirement, duration of insulin required was high ($p<0.05$) (Table 4).

After 1 day of insulin infusion, the drop in TGs was 17–41% (32.8±5.9%), and after 2 days, it was 59–75% (70.4±4.7%). TG was lowered by 72–89% (84.08±3.2%) after 3 days of injection. There was no difference in TG decrease rate between those who started with a higher TG (>5000 mg/dL) and those who started with a lower TG (<5000 mg/dL), $p<0.2$ (Table 5 and Fig. 1).

Hypoglycemia occurred in seven individuals; hypoglycemic episodes ranged from zero to four, and all were treated with a 25% dextrose infusion. Higher dosages and durations of insulin infusion were associated with more hypoglycemic episodes ($p<0.05$). Within 9–25 days (14.0±2.6 days), all patients had recovered. Prolonged hospital stays are associated with more severe pancreatitis and high TG levels ($p<0.05$). All patients were instructed to follow the dietician's diet recommendations when they were discharged. Two patients with TGs <300 mg/dL were given Saroglitazar 4 mg once a day, while the others were given Fenofibrate 160 mg once a day and Saroglitazar 4 mg once a day (n=9). TG levels ranged from 290 to 560 mg/dL (400.6±51.3 mg/dL) after this therapy. Greater admission TG levels lead to higher follow-up levels of TG ($p<0.05$).

Table 2: Laboratory data of the patients

S. No.	Hb (gm)	Total count (Cells/mm^3)	Platelet count (in lakhs)	Sr. creatinine (mg/dL)	Amylase mg/L	CRP mg/L	BSL (R) gm/dL	LFT mg/dL					Lipid profile			
								TB mg/dL	DB mg/dL	ASTU/L	ALTU/L	ALPU/L	TC mg/dL	TG mg/dL	LDL mg/dL	HDL mg/dL
1	10.0	20600	3.2	0.8	510	100	300	1.1	0.4	36	33	56	160	7000	65	35
2	9.3	15000	3.0	1.1	320	56	130	0.9	0.3	40	36	69	125	3600	70	38
3	8.2	13200	1.56	1.2	400	86	126	1.3	0.5	41	38	68	190	4500	66	36
4	9.3	16100	4.2	0.9	600	92	451	1.2	0.4	35	35	66	156	8000	56	40
5	7.8	3800	3.9	0.83	325	62	100	1.1	0.4	39	40	71	188	5400	58	42
6	10.2	16000	4.1	0.66	510	95	144	1.0	0.5	41	39	62	145	8500	65	29
7	11.2	5500	3.2	1.2	210	35	102	1.3	0.3	34	36	75	132	3200	78	34
8	12.0	15200	1.89	0.89	641	110	116	1.4	0.5	38	39	59	140	7700	60	38
9	9.1	4800	2.53	0.77	222	24	320	1.2	0.4	40	40	61	165	2200	58	32
10	7.7	13900	3.20	0.82	300	56	400	1.1	0.4	41	36	66	182	4100	59	40
11	8.9	14500	6.2	1.2	350	88	121	1.2	0.3	36	35	58	130	4600	63	41

Hb: Hemoglobin, CRP: C reactive proteins, BSL (R): Blood sugar level (Random), LFT: Liver function test, TB: Total bilirubin, DB: Direct bilirubin, AST: Aspartate transaminase, ALP: Alkaline phosphatase, ALT: Alanine transaminase, TC: Total cholesterol, TG: Total triglycerides, LDL: Low-density lipoproteins, HDL: High-density lipoproteins

DISCUSSION

HTG etiology may be split into two categories: primary and secondary. While the primary leads to more severe HTG, it may be the interaction of both primary and secondary factors which leads to more severe HTG. In the pregenomic era, severe HTG was usually associated with familial CS (FCS), primary HTG, and mixed HTG, also known as Fredrickson TypeS I, IV, and V, respectively. FCS (I) and mixed HTG (V) cause more severe HTG and frequently occur early, whereas primary HTG (IV) appears in maturity and is generally caused by a secondary factor. Lipoprotein lipase (LPL) deficiency, LPL gene mutation, and Apolipoprotein C II deficiency are all common genetic defects that lead to severe HTG, as are mutations in GPIHBP1 (glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein (1), LMF1, and other genes involved in lipoprotein generation and metabolism) [9].

The precise mechanism through which HTG causes AP is unknown. Excess TGs are converted to FFA by pancreatic lipase, resulting in pancreatic cell damage and ischemia [5,10]. It has also been claimed that hyperviscosity caused by excess TGs in pancreatic capillaries leads to ischemia. HTG-AP has been linked to specific genetic alterations such as CFTR and ApoE gene mutations [2,5]. HTG-induced AP is most likely the consequence of a complicated interaction of several elements, each of which contributes differently in each patient.

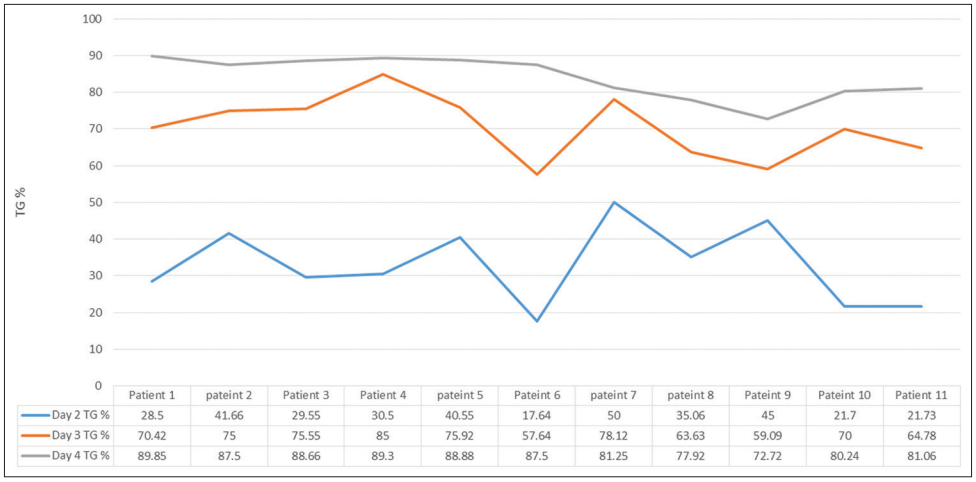

Fig. 1: Triglyceride response to insulin infusion

Table 3: Imaging findings

Sr. No	USG finding	CT	CT severity score	Atlanta class
1	Edematous pancreas with peri-pancreatic fluid collection	The pancreas was bulky with pancreatic necrosis, peri-pancreatic fat stranding, and fluid collection	6	Moderate
2	Edematous pancreas	The pancreas was bulky with peri-pancreatic fat stranding and fluid collection	4	Moderate
3	Edematous pancreas	The pancreas was bulky with peri-pancreatic fat stranding and fluid collection	4	Moderate
4	Edematous pancreas with peri-pancreatic fluid collection	The pancreas was bulky with pancreatic necrosis, peri-pancreatic fat stranding, and fluid collection	6	Moderate
5	Edematous pancreas with peri-pancreatic fluid collection	The pancreas was bulky with peri-pancreatic fat stranding and fluid collection	4	Moderate
6	Edematous pancreas with peri-pancreatic fluid collection	The pancreas was bulky with pancreatic necrosis, peri-pancreatic fat stranding, and fluid collection	6	Moderate
7	Edematous pancreas with fluid collection	The pancreas was bulky with peri-pancreatic fat stranding	2	Mild
8	Edematous pancreas with the peri--pancreatic fluid collection and SMV and PV thrombosis	The pancreas was bulky with pancreatic necrosis, peri-pancreatic fat stranding, and fluid collection, SMV and PV thrombosis	6	Moderate
9	Edematous pancreas	The pancreas was bulky with peri-pancreatic fat stranding	2	Mild
10	Edematous pancreas with peri-pancreatic fluid collection	The pancreas was bulky with peri-pancreatic fat stranding and fluid collection	4	Moderate
11	Edematous pancreas with peri-pancreatic fluid collection	The pancreas was bulky with peri-pancreatic fat stranding and fluid collection	4	Moderate

USG: Ultrasound, CT: Compute tomography

Insulin stimulates LPL activity, which speeds chylomicron breakdown and reduces TG levels [11]. Insulin will help relax pancreatic tissue and may improve immune activity by increasing human leukocyte antigen expression on monocytes and lowering cell death [12]. The previous studies have reported that insulin decreases TG levels by 50–75% over 2–3 days [12,13]. Rebound HTG occurs within 4–5 days of alternate conservative therapy with heparin. Infusions of heparin deplete LPL, resulting in decreased chylomicron catabolism and increased TG levels. With insulin infusion, there was no rebound HTG. TG was serially reduced in our series. Infusion of low molecular weight heparin (LMWH) is equally effective as the infusion of unfractionated heparin [14]. In one case, we utilized LMWH; the insulin infusion required was identical. Plasmapheresis (PEX) quickly eliminates TGs, with a single session required in 80% of patients. Prospective research comparing PEX versus conservative therapy failed to demonstrate a mortality advantage [15]. According to one study, PEX may have a role in the treatment of individuals who have failed conservative treatments such as diet and lipid-lowering agents [16].

Anti-lipid medications using fibrates, statins, niacin, and omega-three fatty acids have been demonstrated to lower TG levels by 36.3%, 10% to 18%, 20%, and 25–33.8%, respectively [17,18]. We utilized fenofibrate 160 mg OD and saroglitazar 4 mg OD either together or separately. Our study showed varied results with food management and oral anti-lipid medications. In three cases, the TG levels increased by up to 22% over the beginning TG levels. TG is lowered by 1–65% in eight patients by oral anti-lipids medications.

Patients with high TGs levels >2648 mg/dL had a higher incidence of local complications, such as acute pancreatic fluid collections on CT scan (69 % vs. 45 %, p=0.002), moderate to severe pancreatitis (74.3% vs. 50%, p=0.005), and more than three organ failures (10% vs. 0%, p=0.008) than those with low TGs levels (1000–2648 mg/dL) [19].

HTG is more common in diabetics and obese patients but Primary HTG can occur without these risk factors also [20]. In our case series, however, all of the patients had mild to moderate pancreatitis with no short- or long-term organ failure. Mild pancreatitis was found in two patients with TG levels <3200 mg/dL, while moderate pancreatitis was

Table 4: Treatment given

S. No.	Wt.	Day 1 TG mg/dL	Insulin infusion U/kg/h	Day 2 TG mg/dL	Insulin infusion U/kg/h	Day 3 TG mg/dL	Insulin infusion U/kg/h	Day 4 TG mg/dL	Insulin infusion U/kg/h	Day 5 TG mg/dL	No. of days insulin required	Total insulin required (U)	No.of hypoglycaemic attack	Oral anti-lipid drugs given after in-hospital treatment	Follow up TG mg/dL after 15 days
1	60	7000	0.1	5000	0.2	2070	0.2	710	0	600	3	720	2	Fenofibrate 160 mg OD and Saroglitazar 4 mg OD	510
2	62	3600	0.1	2100	0.1	900	0	450	0	360	2	297	0	Saroglitazar 4 mg OD	310
3	58	4500	0.1	3170	0.2	1100	0.1	510	0	500	3	556	3	Fenofibrate 160 mg OD and Saroglitazar 4 mg OD	360
4	60	8000	0.1	5560	0.2	1200	0.1	856	0	452	3	720	4	Fenofibrate 160 mg OD and Saroglitazar 4 mg OD	425
5	58	5400	0.1	3210	0.1	1300	0.1	600	0	410	3	417	1	Fenofibrate 160 mg OD and Saroglitazar 4 mg OD	398
6	53	8500	0.1	7000	0.2	3600	0.2	1500	0.1	750	4	763	3	Fenofibrate 160 mg OD and Saroglitazar 4 mg OD	560
7	63	3200	0.1	1600	0.1	700	0	600	0	744	2	300	0	Saroglitazar 4 mg OD	296
8	70	7700	0.1	5000	0.2	2800	0.2	1700	0.1	430	4	1008	4	Fenofibrate 160 mg OD and Saroglitazar 4 mg OD	360
9	51	2200	0.1	1300	0.1	900	0	600	0	400	2	244	0	Saroglitazar 4 mg OD	290
10	55	4100	0.1	3210	0.1	1230	0.1	810	0	610	3	396	0	Fenofibrate 160 mg OD and Saroglitazar 4 mg OD	502
11	53	4600	0.1	3600	0.2	1620	0.1	870	0	520	3	508	1	Fenofibrate 160 mg OD and Saroglitazar 4 mg OD	396

Table 5: Triglyceride levels response to insulin infusion

Sr. no	Day 1 TG mg/dL	Day 2 TGmg/dL	Day 2 drop in TG %	Day 3 TG mg/dL	Day 3 drop in TG %	Day 4 TGmg/dL	Day 4 drop in TG %
1	7000	5000	28.5	2070	70.42	710	89.85
2	3600	2100	41.66	900	75	450	87.5
3	4500	3170	29.55	1100	75.55	510	88.66
4	8000	5560	30.5	1200	85	856	89.3
5	5400	3210	40.55	1300	75.92	600	88.88
6	8500	7000	17.64	3600	57.64	1500	87.5
7	3200	1600	50	700	78.12	600	81.25
8	7700	5000	35.06	2800	63.63	1700	77.92
9	2200	1300	45	900	59.09	600	72.72
10	4100	3210	21.7	1230	70	810	80.24
11	4600	3600	21.73	1620	64.78	870	81.06

seen in two patients with TG levels >3200 mg/dL. Due to the small number of patients, the results may not be comparable.

All of the patients recovered from AP and were discharged with only minor local residual disease. In HTIP, mortality ranges from 0.5% in mild pancreatitis to 5–30% in severe pancreatitis.

CONCLUSION

Insulin infusion is an effective and cost-effective therapy for HTIP. There is no rebound increase in TG as heparin therapy. The TG level dropped significantly in just 3 days, with no serious complications. Hypoglycemia, the most common treatment-related consequence, resolves quickly with dextrose infusion.

AUTHORS' CONTRIBUTION

Dr. Dadasaheb Maindad who is the first order conceived and designed this study. Other authors provided guidance in study conduction and manuscript editing.

CONFLICT OF INTERESTS

The authors confirm that the content of the article has no conflict of interest.

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Nil.

PATIENT CONSENT

Taken.

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