



## The effects on diet, anastomotic type, and loxiglumide on gastric emptying following gastrojejunostomy<sup>☆</sup>

Tayfun Yucel<sup>a</sup>, Dogan Gonullu<sup>b</sup>, Ahmet Orhan Gurer<sup>c</sup>, Ruhan Duzman<sup>d</sup>, Ferda Nihat Koksoy<sup>b,\*</sup>, Necati Yilmaz<sup>e</sup>, Mustafa Sit<sup>f</sup>

<sup>a</sup> Sakarya University, Sakarya Medical School, Department of Surgery, Sakarya, Turkey

<sup>b</sup> Ministry of Health, Taksim Training and Research Hospital, Department of Surgery, Istanbul, Turkey

<sup>c</sup> Ministry of Health, Birecik State Hospital, Department of Surgery, Birecik, Urfa, Turkey

<sup>d</sup> Ministry of Health, Elazig State Hospital, Department of Surgery, Elazig, Turkey

<sup>e</sup> Ministry of Health, Taksim Training and Research Hospital, Department of Nuclear Medicine, Istanbul, Turkey

<sup>f</sup> Ministry of Health, Dogubayazit State Hospital, Department of Surgery, Dogubayazit, Agri, Turkey

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### ABSTRACT

**Purpose:** The effects on gastric emptying of feeding with a normal diet (ND), an early high-calorie and hyperosmolar diet (HCHOD) or normal diet plus intraperitoneal loxiglumide (LOX) were investigated in rats with antecolic (ACGJ) or retrocolic (RCGJ) gastrojejunostomy.

**Methods:** Sixty rats were separated into six groups of ten animals each (ACGJ + ND, RCGJ + ND, ACGJ + HCHOD, RCGJ + HCHOD, ACGJ + ND + LOX, and RCGJ + ND + LOX). On the seventh day, scintigraphic measurements of solid gastric emptying were made at 1, 30 and 60 min.

**Results:** According to the 60-min results, the RCGJ + ND group exhibited delayed emptying compared to the ACGJ + ND group ( $p = 0.023$ ). Gastric emptying of ACGJ + HCHOD rats was delayed compared with the other ACGJ groups (compared to ACGJ + ND:  $p = 0.000$ , and ACGJ + ND + LOX:  $p = 0.015$ ). Gastric emptying was more effective in the RCGJ + ND + LOX group than the other RCGJ groups (compared to RCGJ + ND:  $p = 0.003$ , and RCGJ + HCHOD:  $p = 0.001$ ).

**Conclusion:** Antecolic gastrojejunostomy provided better gastric emptying. An early high-calorie and hyperosmolar enteral diet delayed gastric emptying in both types of anastomosis.

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### 1. Introduction

Gastrojejunostomy has frequently been used for palliative purposes in delayed gastric emptying,<sup>1–3</sup> which can reach a frequency of 67% due to periampullary tumors, and as an additional procedure in surgery for peptic ulcer and gastric and pancreatic tumors.

It was found that delayed gastric emptying occurs at frequency of up to 57% in periampullary cancer cases with palliative gastrojejunostomy and can last for 31 days.<sup>4</sup>

According to a meta-analysis by Lytras in 2007,<sup>5</sup> it is still necessary to indicate the effects of antecolic or retrocolic gastrojejunostomy on gastric emptying. Although an early high-calorie and hyperosmolar enteral diet has frequently been used, its effects on gastric emptying are not yet precisely known, and there is no prokinetic agent with a high level of proof that can be used in patients who suffer from delayed gastric emptying.<sup>5</sup>

Cholecystokinin (CCK), which is a gastrointestinal peptide secreted after meals, has a major role in the regulation of gastric motor function.<sup>6–8</sup> It was shown that an infusion of CCK delays gastric emptying and that blockage of CCK receptors with a specific antagonist such as loxiglumide can reduce it.<sup>9–12</sup>

In our experimental study, we investigated the effects of diet and loxiglumide administration on gastric emptying after antecolic and retrocolic gastrojejunostomy in rats, using solid phase scintigraphy which is the gold standard for measuring gastric emptying.<sup>13</sup>

<sup>☆</sup> The study was conducted at Taksim Training and Research Hospital, Istanbul, Turkey.

\* Corresponding author at: Taksim Egitim ve Arastirma Hastanesi, 1. Genel Cerrahi Klinigi, Cihangir, Beyoglu, 34433 Istanbul, Turkey. Tel.: +90 212 2524300 (office), +0532 4263515 (mobile).

E-mail address: [ferdakoksoy@yahoo.com](mailto:ferdakoksoy@yahoo.com) (F. Nihat Koksoy).

## 2. Materials–methods

This study was performed according to the Helsinki declaration.

Sixty adult Wistar-Albino rats (12 weeks old) (male and female) weighting between 175 and 250 g were used in the study. The animals were adapted to the laboratory conditions for 15 days before the study commenced. They were housed in 12 separate cages containing five animals each at room temperature (24 °C). The animals were fed with dry pellet food and water, and were not given any food for 6 h before the surgery.

The rats were separated into six groups, with ten animals in each group (Fig. 1).

Group A1 underwent antecolic (AC) gastrojejunostomy (GJ) and received a normal diet (ND).

Group R1 underwent retrocolic (RC) GJ and received ND.

Group A2 underwent ACGJ and received a high-calorie and hyperosmolar diet (HCHOD).

Group R2 underwent RCGJ and received HCHOD.

Group A3 underwent ACGJ and received ND and intraperitoneal (IP) loxiglumide (LOX).

Group R3 underwent RCGJ and received ND and IP LOX.

Surgery was carried out while wearing 2.5× magnifying spectacles. After anesthesia administration (diethyl ether inhalation), the skin was shaved and sterilized with a povidon-iodide solution, then a 3-cm median laparotomy was performed.

For ACGJ, a jejunum loop selected distal to the duodenojejunal junction was brought in the antecolic and isoperistaltic direction, and was fixed into the front edge of the greater curvature of the distal stomach. Gastrotomy and enterotomy of approximately 0.5 cm were performed and gastrojejunostomy was completed with one layer of 6/0 polypropylene continuous sutures.

For RCGJ, a jejunum loop was inserted through a window opening meso to the colon and brought to the level of the distal stomach section at the posterior edge of greater curvature in isoperistaltic direction and fixed. A gastrotomy and enterotomy of approximately 0.5 cm were performed, and gastrojejunostomy was completed with one layer of 6/0 polypropylene continuous sutures.

The abdominal wall was closed with 2/0 polypropylene continuous sutures and surgery was completed.

The rats were kept in separate cages during the postoperative period. To minimize any infection risk, sawdust was renewed daily

from the bottom of the cages. During the first 3 postoperative days, the abdominal skin was cleaned daily with povidone-iodide solution.

The rats in groups A1 and R1 were not given any oral food on the first day after surgery, but were injected IP with 1 cc of 5% dextrose. On the second day they were fed with 5% dextrose and water, and on the third day they were fed with normal water and dry pellets ad libitum.

The rats in groups A2 and R2 were not given any oral food on the first day, but were injected IP with 1 cc of 5% dextrose. Starting from the second day, liquid HCHOD of 1.5 kcal/g<sup>14</sup> (Ensure Plus®, Abbott; 680 mOsm/L; 57.0% carbohydrate, 28.2% fat, 14.8% protein; 240 kcal/kg body wt./day;) was given orally daily (by oro-gastric cannule without disturbing the free movement) and the rats were allowed to consume water and dry pellet ad libitum. This diet program was applied for 5 days.

The rats in groups A3 and R3 were not given any oral food on the first day, but were injected IP with 1 cc of 5% dextrose. On the second day, they were fed with 5% dextrose and water; on the third day they were fed with normal water and dry pellets ad libitum. In addition, 0.3 mg/kg CR1505 (loxiglumide) supplied by Rottapharm (Rotta Research Laboratorium, Monza, Italy) was administered IP daily after surgery.<sup>15</sup>

On the seventh day,<sup>16</sup> scintigraphic assessment to determine the rate of solid gastric emptying was started between 13:00 and 15:00 h after the rats had been fasting for 6 h.

The animals were sedated by ethyl ether inhalation and were given 1.5% methylcellulose<sup>17</sup> (1.5 ml heated to 37 °C) containing a solid particle mixture 5mCi Tc<sup>99m</sup> pertechnetate including unabsorbed phenol red (0.5 mg/ml) using a 6-gauge feeding tube. Immediately after application, the animals were kept in a supine position on a gamma camera (Siemens, Scintiview SP, Munich, Germany) on which a parallel-perforated collimator was fixed. Scintigraphic images in an supine position were then recorded for 1 min.

The rats were allowed to move freely in their cages and then placed under the collimator after 30 and 60 min and scintigraphic measurements were recorded (the rats were slightly anesthetized for 1 min at 30 min and 60 min again).

Activity of 200 000 counts recorded for all rats in the 1st minute was taken as the baseline and measurements at 30 and 60 min

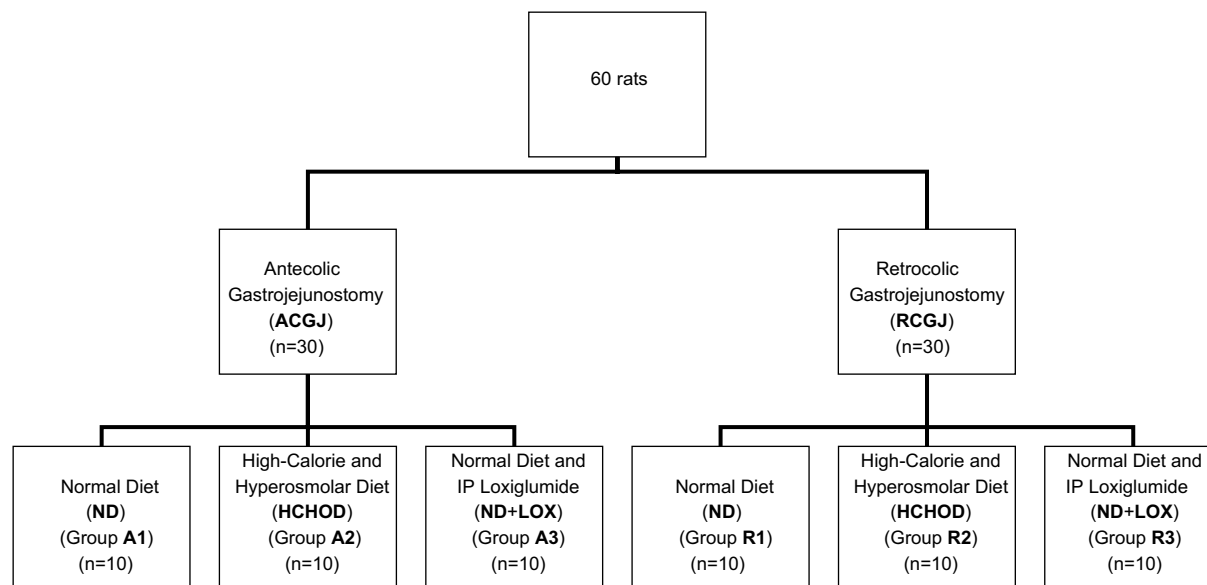


Fig. 1. Flow chart of the groups and the sub-groups.

**Table 1**The means ( $\pm$  SD) of 1st, 30th, 60th min of scintigraphic measurements of solid gastric emptying in groups ( $\times 1000$ ).

Min	Group A1	Group R1	Group A2	Group R2	Group A3	Group R3
1st	200 $\pm$ 0.0	200 $\pm$ 0.0	200 $\pm$ 0.0	200 $\pm$ 0.0	200 $\pm$ 0.0	200 $\pm$ 0.0
30th	173.5 $\pm$ 18.6	183.6 $\pm$ 12.7	191.7 $\pm$ 5.7	186.0 $\pm$ 9.8	179.2 $\pm$ 16.0	167.6 $\pm$ 17.8
60th	147.7 $\pm$ 24.2	173.6 $\pm$ 14.6	185.0 $\pm$ 7.6	175.7 $\pm$ 10.8	152.9 $\pm$ 30.2	145.0 $\pm$ 16.2

A1: Antecolic gastrojejunostomy (ACGJ) and normal diet (ND); R1: Retrocolic GJ (RCGJ)+ND; A2: ACGJ+ high-calorie-hyperosmolar diet (HCHOD); R2: RCGJ + HCHOD; A3: ACGJ + ND and intraperitoneal loxiglumide (LOX); R3: RCGJ + ND + LOX.

involved counting for 1 min. By drawing the area of interest for activity in the stomach and applying this to all recorded images, time-activity corresponding to emptying of the initial stomach activity were obtained for the study interval.

Statistical analysis was performed using SPSS for Windows version 10.0. Radionuclide data obtained according to times for each sub-group were evaluated using the Kruskal–Wallis test and significant differences were detected using the Mann–Whitney *U* test. The statistical significance after Bonferroni correction for three-group comparisons was  $p < 0.016$ . For comparison of two groups,  $p < 0.05$  was considered statistically significant.

### 3. Results

Wound healing was normal in all study groups and all rats survived until day 7, when scintigraphic assessments were made. In terms of body weight, no statistical difference was observed among all the groups ( $p = 0.981$ ).

Average total gastric radioactivity data for all groups at 1, 30 and 60 min are listed in Table 1. The statistical evaluation of radionuclide data for the groups as a function of time is summarized in Table 2.

It is clear from the results that the gastric radionuclide content for all groups significantly decreased in the period between 1 and 30 min. Stomach emptying was rapid in the first 30 min and then relatively slowed down. The decrease between 30 and 60 min was only significant for group R3 ( $p < 0.009$ ).

Comparisons of the 30- and 60-min values of the groups are given in Tables 3 and 4. There were no significant differences in the values at 30 min between the anastomosis and diet-groups.

The 60-min results for the two anastomosis types (Table 3) revealed that the RCGJ + ND group had delayed emptying compared to the ACGJ + ND group ( $p = 0.023$ ).

Comparison of the 60-min results for the diet types (Table 4) indicates that gastric emptying in ACGJ + HCHOD rats was delayed

compared to the other ACGJ groups (compared to ACGJ + ND:  $p = 0.000$ , and ACGJ + ND + LOX:  $p = 0.015$ ), and the RCGJ + ND + LOX group was better than the other RCGJ groups (compared to RCGJ + ND:  $p = 0.003$ , and RCGJ + HCHOD:  $p = 0.001$ ).

In the RCGJ groups, the 60-min results demonstrate that gastric emptying was almost identical ( $p = 0.988$ ) in the groups that received ND and HCHOD.

Gastric emptying results for all groups are shown in Fig. 2.

### 4. Discussion

Gastrojejunostomy can be indicated in mechanical and functional insufficiency of gastric emptying and is frequently used to provide gastroenteric permanence.<sup>18</sup> In addition, despite the availability of improved treatment procedures, gastrojejunostomy is used for duodenal ulcers,<sup>19,20</sup> chronic pancreatitis,<sup>18,21</sup> Crohn's disease,<sup>22</sup> congenital duodenal obstructions (atresia, webs, duplication, annular pancreas), posttraumatic mechanical narrowness, and some systemic diseases such as diabetes mellitus, collagen-vascular diseases and autonomic neuropathies with delayed gastric emptying that do not respond to medical treatment.<sup>18</sup>

In measuring of gastric emptying there are several methods such as scintigraphy, ultrasonography, <sup>13</sup>C-breath testing, magnetic resonance imaging, swallowed capsule telemetry and antroduodenal manometry.<sup>23</sup> Scintigraphy is the gold standard and liquid test meals are not useful because liquid may empty normally when a solid test meal reveals evidence of quite profound gastroparesis.<sup>23</sup> Because of these, we employed solid technic.

There are reports in the literature suggesting that ACGJ and RCGJ applied after gastrectomy do not differ in terms of gastric emptying,<sup>24,25</sup> and other studies indicate that RCGJ operations tend to cause obstruction<sup>26</sup> and that ACGJ should be preferred because it is technically easier and has a shorter application time.<sup>27</sup> There are also studies that suggest that RCGJ has a better effect on gastric emptying.<sup>28,29</sup> The results of a 2007 meta-analysis suggest that ACGJ is preferable, although the evidences for comparison of ACGJ and RCGJ had a rather low level of reliability.<sup>5</sup>

Our study results indicate that ACGJ + ND group exhibited a better result ( $p = 0.023$ ) with regard to gastric emptying

**Table 2**Results of statistical analysis of scintigraphic measurements of solid gastric emptying according to the time within groups ( $p < 0.016$  values are significant).

Group	Minutes	Mean Df.	K.W.(p)	M.W.U (p)
A1	1–30	26,500	0000	0000
	30–60	25,800		NS
R1	1–30	16,400	0000	0000
	30–60	10,000		NS
A2	1–30	8300	0000	0002
	30–60	6700		NS
R2	1–30	14,000	0000	0000
	30–60	20,300		NS
A3	1–30	20,800	0000	0000
	30–60	26,300		NS
R3	1–30	32,400	0000	0000
	30–60	22,600		0009

Mean Df., Mean difference; K.W., Kruskal–Wallis test; M.W.U, Mann–Whitney *U* test; NS, Not significant.

A1: Antecolic gastrojejunostomy (ACGJ) and normal diet (ND); R1: Retrocolic GJ (RCGJ)+ND; A2: ACGJ+ high-calorie-hyperosmolar diet (HCHOD); R2: RCGJ + HCHOD; A3: ACGJ + ND and intraperitoneal loxiglumide (LOX); R3: RCGJ + ND + LOX.

**Table 3**Results of statistical analysis of scintigraphic measurements of solid gastric emptying according to the time of diet-groups ( $p < 0.05$  values are significant).

Min	Diets (anastomosis-groups)			M.W.U (p)
30	A1	R1		NS
	A2	R2		NS
	A3	R3		NS
60	A1	R1		0,023
	A2	R2		NS
	A3	R3		NS

Min, Minutes; M.W.U: Mann–Whitney *U* test.

A1: Antecolic gastrojejunostomy (ACGJ) and normal diet (ND); R1: Retrocolic GJ (RCGJ)+ND; A2: ACGJ+ high-calorie-hyperosmolar diet (HCHOD); R2: RCGJ + HCHOD; A3: ACGJ + ND and intraperitoneal loxiglumide (LOX); R3: RCGJ + ND + LOX.

**Table 4**

Results of statistical analysis of scintigraphic measurements of solid gastric emptying according to the time of anastomosis-groups ( $p < 0.016$  values are significant).

Min	Anastomosis (diet-groups)			K.W (p)		
30	A1	A2	A3	NS		
	R1	R2	R3	NS		
60	A1	A2	A3	0.002	M.W.U	p
					A1–A2	0.000
					A1–A3	NS
					A2–A3	0.015
	R1	R2	R3	0.002	M.W.U	p
					R1–R2	NS
					R1–R3	0.003
					R2–R3	0.001

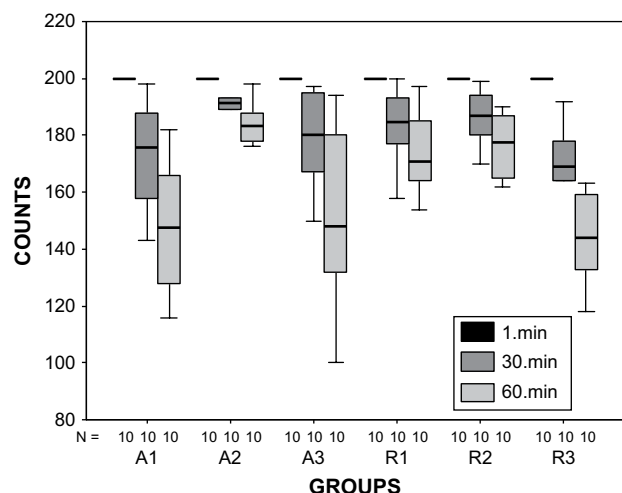
Min, Minutes; K.W., Kruskal–Wallis test; M.W.U, Mann–Whitney U test.

A1: Antecolic gastrojejunostomy (ACGJ) and normal diet (ND); R1: Retrocolic GJ (RCGJ)+ND; A2: ACGJ+ high-calorie-hyperosmolar diet (HCD); R2: RCGJ + HCHOD; A3: ACGJ + ND and intraperitoneal loxiglumide (LOX); R3: RCGJ + ND + LOX.

compared to RCGJ + ND. In addition, rats with RCGJ that received ND and HCHOD had approximately equivalent values ( $p = 0.988$ ). This result is in agreement with a study that found a 42% delay in gastric emptying in periampullary tumor palliative RCGJ,<sup>4</sup> and a meta-analysis revealing that RCGJ is less favorable.<sup>5</sup>

The 60-min results for the ACGJ + HCHOD group revealed a delay compared to the ACGJ + ND group ( $p = 0.000$ ). Comparison of RCGJ + ND and RCGJ + HCHOD led that the latter exhibited a tendency of delayed emptying, but the difference was not significant ( $p = 0.988$ ). These results support the meta-analysis of Lytras,<sup>5</sup> although the author suggested that there are not sufficient studies on the effects of early high-calorie and hyperosmolar liquid enteral nutrition applied after gastric surgery. This result is consistent with other studies<sup>30–32</sup> and suggests that a diet high in calories and osmolality (Ensure Plus®) delays gastric emptying and that such a diet should only be used considering this effect.

In a series of 416 patients with different gastric surgeries, many of which were benign diseases, 24 episodes of delayed gastric emptying were detected and prokinetic agents were used in the treatment of many of these.<sup>33</sup> Many studies have been carried out on prokinetic drugs such as motilin, erythromycin and cisapride to increase gastric motility, but different results have been reported.<sup>5</sup>



**Fig. 2.** The means ( $\pm$  SD) of scintigraphic measurements of solid gastric emptying in groups. A1: Antecolic gastrojejunostomy (ACGJ) and normal diet (ND); R1: Retrocolic GJ (RCGJ) + ND; A2: ACGJ + high calorie-hyperosmolar diet (HCHOD); R2: RCGJ + HCHOD; A3: ACGJ + ND and intraperitoneal loxiglumide (LOX); R3: RCGJ + ND + LOX.

CCK, which is a gastrointestinal peptide, relaxes the stomach fundus, inhibited antral motility and stimulates pyloric contractions. Loxiglumide is a cyclic 5-oxo-pentanoic acid circle that speeds up gastric emptying via specific and competitive CCK-A receptor blockage.<sup>6,34,35</sup>

In our study the LOX sub-groups exhibited better gastric emptying in both ACGJ ( $p = 0.015$ ) and RCGJ ( $p = 0.001$ ) groups. In addition, the RCGJ + ND + LOX sub-group exhibited better emptying than the RCGJ + ND group ( $p = 0.003$ ), which is as an important result. The better results obtained in the LOX groups suggest that this drug can be used in delayed gastric emptying following gastrojejunostomy.

In conclusion, it was found that antecolic gastrojejunostomy provides better gastric emptying. An early high-calorie and hyperosmolar enteral diet can be provided, bearing in mind that it delays gastric emptying.

**Limitation:** Because of there are not the HCHOD + LOX groups it was not understood the effects of loxiglumide on delayed gastric emptying in the HCHOD groups.

#### Ethical approval

Ethical Approval was given by the Ethical Committee of Taksim Training and Research Hospital: No: 061/2008.

#### Conflict of interest

None to declare.

#### Funding

None declared.

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