Gastric emptying of preoperative carbohydrate in elderly assessed using gastric ultrasonography
A randomized controlled study

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Abstract
Background: Preoperative carbohydrate loading enhances postoperative recovery and reduces patient discomfort. However, gastric emptying of liquids can be delayed in elderly populations. Therefore, this study aimed to evaluate the gastric emptying of 400 mL of a carbohydrate drink ingested 2 hours before surgery in elderly patients.

Methods: In this prospective, randomized controlled study, patients aged >65 years were allocated to either fast from midnight (nil per os [NPO] group, n = 29) or drink 400 mL of a carbohydrate drink 2 hours before surgery (carbohydrate group, n = 29). The gastric antrum was assessed using ultrasonography in the supine position, followed by the right lateral decubitus (RLD) position. The gastric antrum was graded as grade 0 (fluid not seen in both positions), grade 1 (fluid only seen in the RLD position), and grade 2 (fluid seen in both positions). The gastric antral cross-sectional area (CSA) and aspirated residual gastric volume were measured.

Results: In 58 patients, the incidence of grade 2 stomach was 13.8% in NPO group and 17.2% in carbohydrate group (P = .790). The gastric antral CSA in the supine position was larger in carbohydrate group than in NPO group (4.42 [3.72–5.18] cm² vs 5.31 [4.35–6.92] cm², P = .018). The gastric antral CSA in the RLD position was not different in NPO and carbohydrate groups (P = .120). There was no difference in gastric volume (2 [0–7.5] vs 3 [0–13.4], P = .331) in NPO group versus carbohydrate group.

Conclusion: The incidence of grade 2 stomach was not different between NPO group and carbohydrate group in elderly patients.

Abbreviations: AP = anteroposterior, ASA = American Society of Anaesthesiologists, BMI = body mass index, CC = craniocaudal, CSA = cross-sectional area, GV = gastric volume, IV = intravenous, NPO = nil per os, RLD = right lateral decubitus, VAS = visual analog scale.

Keywords: carbohydrate, elderly, gastric emptying, gastric ultrasonography

1. Introduction

Pulmonary aspiration is a fatal complication associated with general anesthesia.[1,2] Because an unemptied stomach might predispose pulmonary aspiration, prohibiting oral ingestion before surgery has been accepted as a standard preoperative fasting policy.[1–3] However, a catabolic status caused by prolonged fasting aggravates stress-induced insulin resistance and worsens postoperative outcomes.[4] Thus, many studies have emphasized the disadvantages of unnecessary prolonged fasting and recommended fasting guidelines for minimal or liberal preoperative fasting times.[2,5,6] In line with this new paradigm, carbohydrate drinks, which could be ingested up to 2 hours before surgery, were introduced.[7] These drinks supply energy sources, prevent muscle loss, and maintain the metabolic status.[7,8] Furthermore, carbohydrate drinks reduce perioperative discomforts, such as thirst, hunger, and postoperative nausea and vomiting.[8–10] Therefore, to improve insulin sensitivity, the enhanced recovery after surgery program recommends an intake of at least 45 g of carbohydrate, equivalent to approximately 400 mL of commercially available carbohydrate drinks of 12.5 g/100 mL, 2 hours before anesthetic induction.[5]

In previous studies investigating gastric emptying of preoperative carbohydrates in children, term pregnant women, and adult patients aged approximately 55 years, carbohydrate drinks were emptied within 2 hours of ingestion.[11–13] However, in some elderly patients, gastric emptying of liquids can be delayed due to...
decreased fundic activity,\textsuperscript{14} comorbid diseases, and polypharmacy.\textsuperscript{15} Moreover, since the incidence of gastroesophageal reflux increases with age, the prevalence of undiagnosed gastroesophageal reflux also increases with age.\textsuperscript{16} However, it is unclear whether gastric emptying of 400 mL of a carbohydrate drink 2 hours before surgery is delayed in elderly patients.

Therefore, we designed our study to investigate the gastric emptying of 400 mL of a carbohydrate drink in elderly patients undergoing general anesthesia using gastric ultrasonography. Semiquantitative 3-point grading system (grade 0; empty stomach, grade 1; stomach with negligible fluid, and grade 2; stomach beyond safe limits) were used for assessment of gastric emptying.\textsuperscript{17} Our primary outcome was the incidence of grade 2 stomach in the patients loaded with 400 mL of carbohydrate 2 hours before surgery compared with the patients fasted from midnight.

2. Methods

2.1. Study participants

This study was a prospective randomized controlled study. Written informed consent was obtained from all participants who participated in this trial after approval from the Ethics Committee (KBSMC IRB No. 2019-04-10-013). This trial was registered before patient enrolment at ClinicalTrials.gov (NCT 04159636). The study was conducted and the data were collected in the waiting area and the operating room in a single tertiary hospital (Kangbuk Samsung Hospital). Patients aged >65 years who were scheduled to undergo elective urologic surgery under general anesthesia and had an American Society of Anesthesiologists (ASA) physical status class of I or II were included. The exclusion criteria were as follows: diagnosed for a coexisting disease that delays gastric emptying (e.g., obesity, body mass index [BMI] >30 kg/m\textsuperscript{2}, diabetes, hiatal hernia, gastroesophageal reflux disease, ileus, or enteral tube feeding), history of upper abdominal surgery including gastric surgery, psychiatric or mental disorders, alcoholism, or drug abuse.

2.2. Randomization and blinding

The participants were randomly allocated to either the nil per os (NPO) group (n = 29) or the carbohydrate group (n = 29) in a 1:1 ratio. Randomization allocation was performed using a computer-generated randomization table using a random block (http://www.randomization.com), and the allocated group was kept in a concealed envelope according to the order. One day before surgery, a research assistant allocated participants into each group by opening the concealed envelope in order. The examiners performing gastric ultrasonography were blinded to the group allocation throughout the study period.

2.3. Study protocol

All patients in both groups were allowed to intake both solid and liquid foods until midnight. They had their dinner meals as their last solid intake. Drinking water or other liquids was permitted until midnight in both groups. After midnight, the patients in the NPO group were kept fasted until surgery including water. The fasting policy in the NPO group followed our standard preoperative fasting guidelines, which limit the oral intake including water after midnight until surgery. The carbohydrate group was asked to ingest 400 mL of a carbohydrate drink (NPO, Daesang WelLife Co., Ltd., South Korea; 12.8% carbohydrates, 50 kcal/100 mL, 290 mOsm/kg) 2 hours before anesthesia induction. Drinking liquids other than the carbohydrate on the day of surgery was not allowed in the carbohydrate group.

2.4. Ultrasonographic assessment of the stomach

After the participants arrived in the waiting area, gastric ultrasonography was performed by 2 staff anesthesiologists (EAC and JGS). Both anesthesiologists were experienced in gastric ultrasonography (>100 cases). A standard abdominal setting and a low-frequency curved array transducer (1.6–4.6 MHz) was used with the ultrasonography device (LogiQ E, GE Healthcare, Piscataway, NJ). Gastric ultrasonography was performed in the supine position with a 45° head-up tilt, followed by a 45° semi-sitting right lateral decubitus (RLD) position. In both positions, the gastric antrum was detected in the epigastrium in the parasagittal plane. The gastric antrum was located between the left lobe of the liver and the pancreas head, anterior to the inferior vena cava, and the superior mesenteric vein. The probe was adjusted to obtain the smallest round shape of the gastric antral cross-section.

The gastric antrum was evaluated qualitatively and quantitatively. For qualitative assessment, the gastric antrum was assessed for its nature of content—empty, fluid, or solid. Based on the qualitative assessment, the gastric antrum was classified into 3 grades using a semiquantitative 3-point grading system—grade 0, fluid not seen in both positions; grade 1, fluid only seen in the RLD position; and grade 2, fluid seen in both positions.\textsuperscript{17}

For qualitative assessment, 2 perpendicular diameters were obtained between the peristalsis, including the serosa layers, which were the anteroposterior and the craniocaudal (CC) diameters. The gastric antral cross-sectional area (CSA) was calculated by the area of an ellipse formula: \( \text{CSA} = \frac{\pi \times \text{AP} \times \text{CC}}{4} \) (Fig. 1A).\textsuperscript{18}

2.5. Anesthetic induction and other outcomes assessments

After the ultrasonographic assessment, hunger, thirst, and anxiety were assessed by other researchers. The degree of preoperative hunger, thirst, and anxiety were evaluated using the visual analogue scale (VAS) scores ranging from 0 (not at all) to 10 (very much). The time from the last oral intake to the ultrasonographic assessment was also assessed. After all assessments were completed in the waiting area, the patient underwent a standard preoperative patient confirmation procedure (which usually takes around 30 minutes) and was then transferred to the operating room for anesthesia induction.

Anesthesia was performed by the anesthesiologist blinded to the group allocation. Patients other than grade 2 stomach were induced with intravenous (IV) propofol 1 to 1.5 mg/kg, and rocuronium 0.6 to 0.8 mg/kg IV was given for paralysis. The anesthesiologist was warned once the grade 2 stomach was detected in the waiting area. In case of grade 2 stomach, the patient was induced using rapid sequence induction. The rapid sequence induction was conducted after preoxygenation with 100% oxygen for 5 minutes, giving propofol 1 to 1.5 mg/kg IV, and 1 mg/kg of rocuronium IV. Cricoid pressure was applied, and
the airway was secured after 90 seconds without mask ventilation. The airway was secured with either i-gel (Intersurgical Ltd., Wokingham, UK) or an endotracheal tube, according to the expected operation time. For the aspiration of gastric contents, a 12-French orogastric ST probe (Lucky Medical Co., Ltd., Seoul, South Korea) was inserted into the stomach through the side channel of the i-gel or the oropharyngeal airway of the endotracheal tube. The ST probe accompanies a suction hole at the tip, which allows the suctioning of gastric contents while monitoring the core temperature. After confirming the position of the ST probe tip in the gastric antrum using gastric ultrasonography, a 50-mL syringe was connected to the ST probe (Fig. 1B). Residual gastric contents were aspirated, and the amount of residual gastric volume (GV) was recorded. GV was divided by weight (GV/kg), and the incidence of GV/kg >1.5 mL/kg was collected. The acidity of gastric content was measured by using a pH meter (S2K712, ISFET Co., Ltd., Saitama, Japan).

2.6. Statistical analysis
The primary outcome of our study was the incidence of grade 2 stomach in both groups. The sample size estimation was based on our preliminary study collected consecutively \( n = 26 \), in which the incidence of grade 2 stomach was 38.5% in the carbohydrate group and 7.7% in the NPO group (not published). The sample size was estimated to detect a 30.8% difference in the incidence of grade 2 stomach in our preliminary study. A minimum sample size of 58 subjects (29 in each group) was required with 80% power and a 0.05% level, considering a dropout rate of 0.1%.

Data for continuous variables are presented as mean± standard deviation for the normally distributed data, and median (interquartile range) for the non-normally distributed data, and categorical variables are presented as number and percentage. For primary outcome analysis, the chi-square test was used to compare the incidence of grade 2 stomach in both groups. The secondary outcomes were compared using Student t test (CSA_{RLD}, VAS score for anxiety, hunger, and thirst), Mann–Whitney U test (CSA_{supine}, GV, GV/kg, and pH) or the chi-square test (incidence of GV/kg >1.5 mL/kg). A P-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, New York, NY).

3. Results
Seventy-three patients were assessed for eligibility from January 2020 to August 2020. A total of 15 patients were excluded, 13 patients did not meet the inclusion criteria, and 2 patients declined to participate in our study. Fifty-eight patients were randomly allocated to either the NPO group or the carbohydrate group. All patients in both groups received the allocated intervention. No patient was lost to follow-up. Therefore, 58 patients (29 patients in each group) were analyzed (Fig. 2).

The baseline characteristics of our study population are described in Table 1. There were no differences in age, sex, height, weight, body mass index, ASA class, incidence of hypertension, smoking history, and operation type between the NPO and carbohydrate groups. Fasting hours for solids was for 16.2±3.4 hours in the NPO group and 16.7±4.7 hours in the carbohydrate group (\( P = .633 \)). Patients in the NPO group fasted for liquids for 12.3±5.1 hours, and those in the carbohydrate group fasted for liquid for 2.2±1.2 hours (\( P < .001 \)).

Semiquantitative 3-point stomach grades were compared between the 2 groups. Four (13.8%), 7 (24.1%), and 18 (62.1%) patients were classified into grades 2, 1, and 0, respectively, in the NPO group. In the carbohydrate group, 5 (17.2%), 5 (17.2%), 19 (65.5%) patients classified into grades 2, 1, and 0, respectively. The incidence of grade 2 stomach between the 2 groups was not significantly different (13.8% in the NPO group and 17.2% in the carbohydrate group, \( P = .790 \); Fig. 3).

The gastric antral CSA in the supine position was smaller in the carbohydrate group (4.42 [3.72–5.18] cm²) than in the carbohydrate group (5.31 [4.35–6.92] cm², \( P = .018 \)), with a mean difference (95% confidence level [CI]) of −1.43 (−2.77 to −0.08). The gastric antral CSA in the RLD position was 6.63±2.77 cm² in the NPO group and 7.97±3.62 cm² in the carbohydrate group (\( P = .120 \)), with a mean difference (95% CI) of −1.35 (−3.05–0.36). There was no solid content observed in our study subjects. There was no difference in the nature of the content between the 2 groups (\( P = .785 \)). In the NPO group, 2 (0–7.5) mL of gastric contents was aspirated from patients’ stomach, while in the carbohydrate group, 3 (0–13.4) mL of gastric contents was aspirated from patients’ stomach (mean difference: −9.56; 95% CI: −19.10 to −0.02; \( P = .331 \)). The GV/kg was 0.03 (0–0.12) mL/kg in the NPO group and 0.04 (0–0.18) mL/kg in the carbohydrate group (mean difference: −0.15; 95% CI: −0.30–0; \( P = .356 \)). The incidence of
GV/kg >1.5 mL/kg was 3.4% in the carbohydrate group and 0% in the NPO group \( (P > .999) \). Gastric pH was higher in the carbohydrate group (2.8 [1.6–5.3]) than in the NPO group (1.7 [1.3–2.7]; \( P = .020 \)). There was no case of regurgitation of gastric contents in either of the groups (Table 2). Figure 4 describes the box plots of CSA, GV, and GV/kg. The highest value of GV, and GV/kg were 94 mL, and 1.56 mL/kg in the carbohydrate group, respectively.

Preoperative anxiety, hunger, and thirst scores were compared using the VAS between the 2 groups and are presented in Table 3. The anxiety score was not different between groups (3.1 ± 2.9 in the NPO group and 4.0 ± 3.4 in the carbohydrate group; \( P = .280 \)). The hunger score was lower in the carbohydrate group than in the NPO group (1.3 ± 2.2 vs 4.2 ± 2.6; \( P < .001 \)). The thirst score was also lower in the carbohydrate group than in the NPO group (1.6 ± 2.1 vs 4.5 ± 2.4; \( P < .001 \)).

Table 1

|                | NPO group (n = 29) | Carbohydrate group (n = 29) | \( P \)-value |
|----------------|-------------------|----------------------------|---------------|
| Age, y         | 73.9 ± 5.8        | 73.3 ± 5.4                 | .692          |
| Sex, male      | 24 (82.8%)        | 23 (79.3%)                 | .738          |
| Height, cm     | 163.3 ± 8.5       | 163.3 ± 6.4                | .996          |
| Weight, kg     | 66.3 ± 10.5       | 67.1 ± 10.8                | .799          |
| BMI, kg/m²     | 24.8 ± 2.9        | 25.1 ± 3.1                 | .718          |
| ASA class, I/II| 7/22 (24.1/75.9)  | 9/20 (31.0/69.0)           | .557          |
| Hypertension   | 19 (65.5)         | 13 (44.8)                  | .113          |
| Smoking        | 0 (0)             | 1 (3.4)                    | > .999        |
| Operation type |                   |                            | .104          |
| Nephrectomy    | 1 (3.4)           | 6 (20.7)                   |               |
| Cystectomy     | 2 (6.9)           | 3 (10.3)                   |               |
| Prostatectomy  | 4 (13.8)          | 8 (27.6)                   |               |
| TURB           | 17 (58.6)         | 10 (34.5)                  |               |
| Ureteroureterostomy | 2 (6.9)  | 0 (0)                      |               |
| Ureterolithotomy| 3 (10.3)          | 2 (6.9)                    |               |
| Fasting for solids, h | 16.2 ± 3.4 | 16.7 ± 4.7                 | .633          |
| Fasting for liquids, h | 12.3 ± 5.1 | 2.2 ± 1.2                  | < .001        |

Data are presented as mean ± standard deviation or number (%).

ASA = American Society of Anaesthesiologists, BMI = body mass index, NPO = nil per os, TURB = transurethral resection of bladder tumor.
4. Discussion

The present study assessed gastric emptying of 400 mL of a carbohydrate drink ingested 2 hours before surgery compared with midnight fasting in elderly population. The incidence of grade 2 stomach between the 2 study groups was not different in our study. The gastric antral CSA in RLD position, the amount of aspirated GV, GV/kg, and the incidence of GV/kg > 1.5 mL/kg were not different between the carbohydrate group and the NPO group. Hunger and thirst scores were improved after ingestion of carbohydrate drink.

Carbohydrate loading was introduced to prevent surgical stress-induced insulin resistance and maintain metabolic homeostasis, thereby improving the quality of postoperative recovery and patient satisfaction. Carbohydrate drinks are made of polymers that do not delay gastric emptying compared with monomers. When measured with a gamma camera, 400 mL of a carbohydrate drink was emptied from the stomach after 90 minutes of ingestion in patients undergoing elective surgery. Gastric emptying of carbohydrate drinks was also evaluated using gastric ultrasonography in different study populations (such as term parturient, pediatric patients aged < 18 years, and adult patients aged 55 years on average) scheduled to undergo endoscopic surgery. These studies demonstrated that carbohydrate drinks were emptied after 2 hours of the last ingestion. Therefore, it is generally believed that carbohydrates can be safely ingested up to 2 hours before surgery. However, it is unclear whether this is applicable in patients with coexisting diseases that delay gastric emptying, such as morbid obesity, diabetes, or gastroesophageal reflux. Moreover, it is undetermined whether 400 mL of a carbohydrate drink can be safely ingested by elderly patients who might have predisposing factors for delayed gastric emptying.

The primary outcome of our study was the incidence of grade 2 stomach by the semiquantitative 3-point grading system introduced by Perlas et al. It has been suggested in the previous study that the cut-off value of CSA of 320 mm² can discriminate nonfasted stomach from fasted stomach. However, there is no absolute reference value for the CSA. Moreover, if the cut-off value of 320 mm² had been used in our study, the false positive rate there would have been too high. Thus, we thought that determining the gastric emptying based on specific value of CSA can be debatable. Therefore, we chose to distinguish between emptied and non-emptied stomach based on semiquantitative 3-point grading system. The 3-point grading system can be applied to evaluate fluid contents and has been described as a simple screening tool for discriminating patients with a high-volume stomach. Grade 2 stomach implies that 75% patients are likely to have > 100 mL of gastric fluid, which corresponds to GV/kg > 1.5 mL/kg. The incidence of grade 2 stomach was not different in the NPO and carbohydrate groups (13.8% vs 17.2%). However, the incidence of grade 2 stomach in the NPO group (13.8%) in our study was higher than that reported in the previous studies. Perlas et al. performed a prospective descriptive study on fasted surgical patients and reported that the incidence of grade 2 stomach was 3.5% (7/200). Arzola et al. described that 1% (1 of 103) pregnant fasted women scheduled for elective caesarean section had grade 2 stomach. In severely obese fasted patients, 5.2% (2 of 38) of patients had grade 2 stomach. We believe that the higher incidence of grade 2 stomach in our study was caused by differences in baseline characteristics such as race, eating habits, and age.

In our study, there were 2 patients in the carbohydrate group whose could be considered to be at risk to pulmonary aspiration. One patient was a 69-year-old male patient scheduled to undergo prostatectomy (BMI: 26.8 kg/m²) with the maximum gastric fluid aspirated of 94 mL (1.2 mL/kg). The other patient with GV/kg > 1.5 mL/kg was a 69-year-old female patient (BMI: 23.4 kg/m²) with an underlying spinal stenosis disease undergoing total cystectomy. The aspirated gastric fluid in this patient was 81 mL.

### Table 2

Gastric ultrasonographic assessment, aspirated residual gastric contents, and regurgitation of gastric contents.

|                          | NPO group (n = 29) | Carbohydrate group (n = 29) | Mean difference (95% CI) | P-value  |
|--------------------------|--------------------|-----------------------------|--------------------------|----------|
| **Gastric ultrasound assessment** |                    |                             |                          |          |
| CSA<sub>supine</sub>, cm²  | 4.42 ± 3.72–5.18   | 5.31 ± 3.45–6.92            | 1.43 ± 2.77 to 0.08     | .018*    |
| CSA<sub>RLD</sub>, cm²    | 6.63 ± 2.77        | 7.97 ± 3.62                 | 1.35 ± 3.05 to 0.36     | .120     |
| Empty/Fluid/solid        | 18/11/0 (62.1/37.9/0) | 19/10/0 (65.5/34.5/0)       | 0.12 ± 0.31 to 0.08     | .785     |
| **Aspirated residual gastric contents** |                    |                             |                          |          |
| GV, mL                   | 2 (0–7.5)          | 3 (0–13.4)                  | −9.56 ± 10.10 to 0.02   | .331     |
| GV/kg, mL/kg             | 0.03 (0–0.12)      | 0.04 (0–0.18)               | 0.15 ± 0.30 to 0        | .356     |
| GV/kg > 1.5 mL/kg        | 0 (0)              | 1 (0)                       | > 0.999                 |          |
| pH                       | 1.7 (1.3–2.7)      | 2.8 (1.6–5.3)               | −1.18 ± 2.17 to 0.20    | .042*    |
| Regurgitation of gastric contents | 0 (0)              | 0 (0)                       | N/A                     |          |

Data are presented by mean ± standard deviation, median (interquartile range), or number (%).

CSA = cross-sectional area, GV = gastric volume, N/A = not available, NPO = nil per os, RLD = right lateral decubitus.

* P < .05.
Pulmonary aspiration was not occurred in any of our study patients. Although there is no definite threshold value over which pulmonary aspiration increases, 100mL (1.5 mL/kg) has been commonly used as a volume threshold in previous studies. However, because pulmonary aspiration is multifactorial, it does not always occur even though GV exceeds 100mL or 1.5 mL/kg. Sometimes, multiple factors need to be combined to contribute to pulmonary aspiration, such as difficult airway, inappropriate airway managements causing gas insufflation into the stomach or coughing might lead to regurgitation of gastric contents. However, as the stomach was loaded with a carbohydrate drink and not water, the patient outcomes might worsen when it is aspirated. Therefore, we suggest performing routine gastric ultrasonography prior to anesthesia in elderly patients who are loaded with carbohydrate 400mL 2 hours before surgery for screening of unexpected delayed gastric emptying.

Our study has some limitations. First, the amount of gastric fluid aspirated did not completely represent the full gastric

**Table 3**

|                | NPO group (n = 29) | Carbohydrate group (n = 29) | Mean difference (95% CI) | P-value |
|----------------|--------------------|-----------------------------|--------------------------|---------|
| Anxiety        | 3.1 ± 2.9          | 4.0 ± 3.4                   | -0.9 (-2.5 - 0.8)        | .280    |
| Hunger         | 4.2 ± 2.6          | 1.3 ± 2.2                   | 2.9 (1.7 - 4.2)          | <.001*  |
| Thirst         | 4.5 ± 2.4          | 1.6 ± 2.1                   | 2.9 (1.8 - 4.1)          | <.001*  |

Data are presented as mean ± standard deviation.

NPO = nil per os.

* P < .05.
content volume. The aspiration of gastric fluid was performed in the supine position to avoid disturbing the rapid preparation for the operation. If more vigorous aspiration was performed as in a previous study,[26] more gastric contents might have been aspirated. Second, there was a time interval between the gastric ultrasonographic assessment and aspiration of gastric fluids, which generally took from 30 minutes to 1 hour. Therefore, there might be less gastric fluid aspirated than that expected at the time of gastric ultrasonographic assessment. Third, because we included ASA class I or II in our study population, our study population might not include patients with comorbidities or polypharmacy which would greatly affect gastric emptying of liquids. Therefore, it is unclear whether our results could be extrapolated in patients with severe systemic disease. Fourth, although the 3-point grading system is a simple and useful screening tool, caution may be required when determining the risk of pulmonary aspiration for grade 2 stomach. Because, even though there was no difference between the 2 groups in the incidence of grade 2 stomach, CSA in supine position was greater though there was no difference between the 2 groups in the risk of pulmonary aspiration for grade 2 stomach. Because, even extrapolated in patients with severe systemic disease.

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