Original Article
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Gastric Emptying Scintigraphy: Diagnostic Value of Delayed Imaging and the Impact on Reclassification of Diagnosis

Mide Boşalma Sintigrafisi: Gecikmiş Görüntülemenin Tanısal Değeri ve Tanının Yeniden Sınıflandırılmasına Etkisi

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Abstract

Objectives: To investigate the added diagnostic value of delayed imaging at 3 and 4 h compared to 2 h imaging as well as scanning up to 4 h compared to 3, and by this means, diagnosis reclassification or changes in diagnosis across various time points.

Methods: Seventeen patients clinically suspected of gastroparesis, 8 (47.1%) men and 9 (52.9%) women, according to the standard procedural guidelines, underwent gastric emptying scintigraphy after ingesting a standard meal. One-minute static images in anterior and posterior projections were acquired immediately after ingestion and then at 1-, 2-, 3- , and 4 h time points. For image analysis, a manual region-of-interest was drawn, and then, count of stomach in each projection was used to calculate geometric mean for each time point. Decay correction was applied. At 2-, 3- and 4 h time points, percentage of retained activity was compared to standard values; therefore, each patient was labeled as normal or delayed.

Results: Pairwise correlation between time points was statistically significant. Value of hour 3 shows an extremely strong correlation with the value of hour 4 ($r=0.951$, $p<0.001$). In hour 2, of 17 participants, 11 (64.7%) were diagnosed as normal and 6 (35.3%) as delayed. In hour 3, the diagnosis made as delayed rose to 9 (52.9%), whereas normal was 8 (47.1%). Finally, in hour 4, results were 10 (58.8%) as delayed and 7 (41.2%) as normal. All subjects who were labeled as delayed in hour 3 remained with the same diagnosis and 1 out of 8 subjects categorized as normal in hour 3 changed to delayed. For testing agreement, coefficient of kappa was computed between each pair. Agreement between diagnosis in hour 2 with hours 3 or 4 was not strong (kappa <0.6 for both pairs). However, a strong agreement was found between diagnosis in hours 3 and 4 (kappa: 0.881).

Conclusion: Because of excellent correlation between values of hours 3 and 4 and strong agreement between the diagnosis in those time points, extending acquisition from 3 to 4 h adds little to the final diagnosis and may not be noticeably meaningful, especially in the clinical setting.

Keywords: Gastric emptying scintigraphy, delayed imaging, diagnostic value, reclassification of diagnosis

Öz

Amaç: İkinci saatteki görüntülemeye kıyasla üçüncü ve dördüncü saatteki gecikmeli görüntülemenin ve üçüncü saatteki görüntülemeye kıyasla dördüncü saatteki görüntülemenin tanıya katkısını araştırarak bu sayede tanının yeniden sınıflandırılmasını veya çeşitli zaman noktalarında tanıdaki değişikliklerin tespit edilmesi.

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Yöntem: Standart prosedür kılavuzlarına göre klinik olarak gastroparezi şüphesi olan 8'i (%47,1) erkek ve 9'u (%52,9) kadın 17 hastaya, standart bir yemek yedikten sonra mide boşalma sintigrafisi uygulandı. Anterior ve posterior projeksiyonlardaki bir dakikalık statik görüntüler, yemek yedikten hemen sonra ve ardından 1-, 2-, 3- ve 4 saatlik zaman noktalarında elde edildi. Görüntü analizi için, manuel bir ilgi bölgesi çizildi ve ardından, her bir zaman noktası için geometrik ortalamayı hesaplamak için her projeksiyondaki mide sayısı kullanıldı. Parçalanma düzeltilmesi uygulandı. 2-, 3- ve 4 saatlik zaman noktalarında tutulan aktivite yüzdesi standart değerlerle karşılaştırıldı; bunun için, her hasta normal veya gecikmiş olarak etiketlendi.

Bulgular: Zaman noktaları arasındaki ikili korelasyon istatistiksel olarak anlamlıydı. Üçüncü saat değeri 4. saat değeri ile son derece güçlü bir korelasyon göstermekteydi (r=0,951, p<0,001). İkinci saatte 17 katılımcının 11'i (%64,7) normal, 6'sı (%35,3) gecikmiş olarak teşhis edildi. Üçüncü saatte gecikmiş tanı 9'a (%52,9), normal tanı ise 8'e (%47,1) çıktı. Son olarak, 4. saatte katılımcıların 10'u (%58,8) gecikmiş ve 7'si (%41,2) normal olarak teşhis edildi. Üçüncü saatte gecikmiş olarak etiketlenen tüm denekler aynı teşhiste kaldı ve 3. saatte normal olarak sınıflandırılan 8 kişiden 1'i teşhisi gecikmiş olarak değişti. Uyumu test etmek için, her çift arasında kappa kat sayısı hesaplandı. İkinci saatteki tanı ile 3. veya 4. saatteki tanı arasındaki uyum güçlü değildi (her iki çift için kappa <0,6). Ancak 3. ve 4. saatlerdeki tanı arasında güçlü bir uyum bulundu (kappa: 0,881).

Sonuç: Üçüncü ve dördüncü saat değerleri arasındaki mükemmel korelasyon ve bu zaman noktalarındaki tanılar arasındaki güçlü uyum nedeniyle, görüntülemeyi 3. saatten 4. saate uzatmak nihai tanıya çok az katkıda bulunur ve özellikle klinik uygulamada anlamlı bir etkisi olmayabilir.

Anahtar kelimeler: Mide boşalma sintigrafisi, gecikmiş görüntüleme, tanı değeri, tanının yeniden sınıflandırılması

Introduction

Gastric emptying scintigraphy (GES) is currently the standard and validated method to non-invasively evaluate patients suspected of gastroparesis. This method enables us to quantitatively measure the speed and timing of the emptying function of the stomach (1). Because of the high reliability and reproducibility of GES (1), it helps monitor patients on serial imaging in addition to its role in making the initial diagnosis. The American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine have published consensus recommendations to help health professionals apply standardized protocols of performance and interpretation of GES across the world. Accordingly, imaging at several time points, including 0, 1, 2, 3, and 4 h after ingestion of a low-fat eggwhite meal is recommended as a solution to maximize the sensitivity of the test (2,3). However, there is some uncertainty about the compliance and adherence of nuclear medicine laboratories to follow these guidelines (4). One such issue is the time points at which the images should be acquired. Some centers only perform imaging up to hour 2 post-ingestion, but others extend the duration of imaging to 4 h. There are a number of investigations that have found the superiority of delayed imaging (5,6,7,8). The extent to which delayed imaging, i.e., in 3 and 4 h, improves the diagnostic power of GES is yet to be elucidated. Additionally, the percentage of patients in whom the diagnosis is changed between consecutive time points and the added value of extending the scanning time is almost unknown. In this study, it is intended to investigate the added diagnostic value of delayed imaging at 3 and 4 h and thereby the changes in diagnosis from one time point to another.

Materials and Methods

Study Subjects

Seventeen patients clinically suspected of gastroparesis were referred by a referral gastroenterology center to our laboratory for GES for further evaluation of gastrointestinal symptoms, of whom 8 (47.1%) were male and 9 (52.9%) were female with a mean age of 49.3±21.1, from 15 to 77. All patients were initially examined clinically for their complaints and a thorough pertinent history was taken including prior esophageal and gastric surgeries, current prokinetic medications (metoclopramide, domperidone, etc.) and history of reflux or other esophageal problems. Patients who underwent recent upper endoscopic procedures were excluded from the study. Informed consent was obtained from all participants and the study has been approved by the Affairs-Shahid Beheshti University of Medical Sciences Ethics Committee (approval no: IR.SBMU.RETECH.REC.1402.058, date: 16.04.2023).

Patient Preparation and Study Procedure

According to the standard procedural guidelines and consensus recommendations for performing and interpreting GES, all patients were advised to keep a 4 h period of fasting before imaging and to discontinue taking any prokinetic or anti-motility medications for at least 2 days. Also, blood testing was performed for all participants to measure serum glucose using a glucometer shortly before initiation of the procedure. Those with serum glucose higher than 200-250 mg/dL were excluded. Patients were also asked to abstain from smoking from a few hours before until the end of study. Each patient was provided a standard meal containing the white of 4 eggs, two slices of toasted bread and 30 g or a spoonful of jam and then mixed with 18-20 MBq of Tc-99m-sulfur colloid

cooked in an oven until being firm and patients were instructed to eat the meal, prepared as a small sandwich, within 10 min. Each patient was also given a glass of water (about 200 mL) to help them swallow their meal. Immediately after ingestion of meal, for each patient, 1 min static images (matrix size of 128x128) in anterior and posterior projections of the trunk were acquired (as time 0) using a single-headed gamma camera in an upright position, in a way that their body touched the detector surface. Acquisition was repeated at 1-, 2-, 3- and 4-hour time points post-ingestion for all participants with the same protocol (1,3,4). Patients who were experiencing episodes of vomiting during the procedure were excluded from the study as well. Besides, the process of meal ingestion by patients was monitored uninterruptedly to ensure that the meal was ingested sufficiently. Participants were requested to avoid intense physical activity for usual daily movement.

Image Analysis and Gastric Emptying Calculation

Before analyzing images, all were inspected for quality to ensure that no esophageal reflux or overlapping of the intestinal loop containing radioactivity in the stomach existed. Then, in each projection, a region-of-interest is manually drawn around the stomach (Figure 1). Care was taken not to include interfering intestinal activity. The count of the stomach in each projection was determined. For each time point, the geometric mean was calculated by the following formula: squared root of the product of counts of anterior and posterior projections. For 1-, 2-, 3- and 4 h time points, decay correction was employed using coefficients from the physical decay table of Tc-99m (fraction remaining after 1, 2, 3 and 4 h are 0.891, 0.794, 0.708 and 0.631 respectively) (9). Decay-corrected geometric mean of each time point was divided by that of time 0 so that the percentage of the activity retained in the stomach was computed. At 2-, 3- and 4-hour time points, the percentage of retained activity was compared to standard or reference values (values higher than 90%, 60%, 30% and 10% at 1-, 2-, 3- and 4-hours post-ingestion respectively are considered abnormal) and therefore were labeled dichotomously as normal or abnormal (delayed). The images and the pattern of emptying or approximate curve was observed to ensure proper labeling.

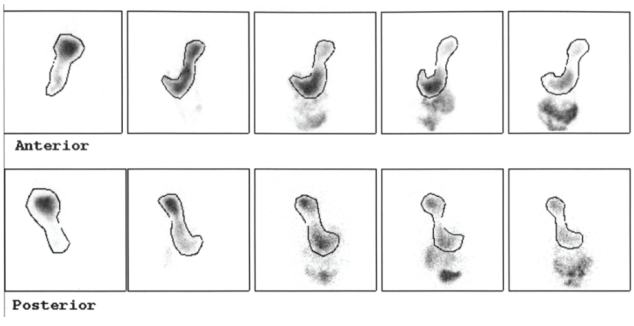

Figure 1. Planar images in anterior and posterior projections at five time points: 0 (immediately after ingestion), 1, 2, 3 h. Regions of interest of the stomach are manually drawn in a way that no other interfering activity gets included in it. Upper and lower rows demonstrate anterior and posterior projections, respectively, from left (hour 0) to right (hour 4)

Statistical Analysis

Mean and standard deviation, median, and quartiles of the percentages retained in the stomach at five time points (0, 1, 2, 3, and 4) were calculated. Error bar plot and box plot were used to display the results. Pairwise correlation testing was conducted between various time points, and Pearson's correlation coefficient was computed and graphed in matrix scatterplot. To compare diagnosis (labeled as normal or delayed) at 2-, 3-, and 4 h time points, an agreement test was employed between pairs and the kappa coefficient was computed. All statistical analyses were conducted and graphs were plotted in the SPSS software package (version 24), and a significance level of 0.05 was considered.

Results

Mean and standard deviation, median, and quartiles of the percentages retained in the stomach at each time point are summarized in Table 1. These values are graphically displayed in the error bar plot and box plot in Figure 2. Pairwise correlations between time points were statistically significant and are presented in Table 2. The value at hour 1 is strongly correlated with that at hour 2 but weak to moderate to those at hours 3 and 4. The value of hour 3 shows an extremely strong correlation with the value of hour 4 ($r=0.951$, $p<0.001$). The correlation coefficients of hour 2 are also moderate to strong with hours 3 and 4. Figure 3 presents the matrix scatterplot. Figure 4 depicts a stacked bar chart for diagnosis at different time points. Diagnosis was determined based on comparison with reference values recommended by standard guidelines. In hour 2 of 17 participants, 11 (64.7%) were diagnosed as normal and 6 (35.3%) as delayed. In hour 3, the diagnosis

Table 1. Values of mean, median, and quantiles of the percentage retained in the stomach at 4 time points

Time point	Mean (SD)	Median	Quartiles		
			25	50	75
Hour 1	75.36 (11.84)	78.00	64.50	78.00	85.00
Hour 2	50.05 (18.42)	56.00	33.00	56.00	67.00
Hour 3	31.28 (20.98)	34.00	8.25	34.00	48.50
Hour 4	21.62 (19.33)	17.00	3.35	17.00	38.75

SD: Standard deviation

Table 2. Results of correlation testing between pairs of time points			
Pairwise correlation between variables		**Correlation coefficient**	**p value**
Hour 1	Hour 2	0.797	0.000
	Hour 3	0.569	0.017
	Hour 4	0.569	0.017
Hour 2	Hour 3	0.756	0.000
	Hour 4	0.727	0.001
Hour 3	Hour 4	0.951	0.000

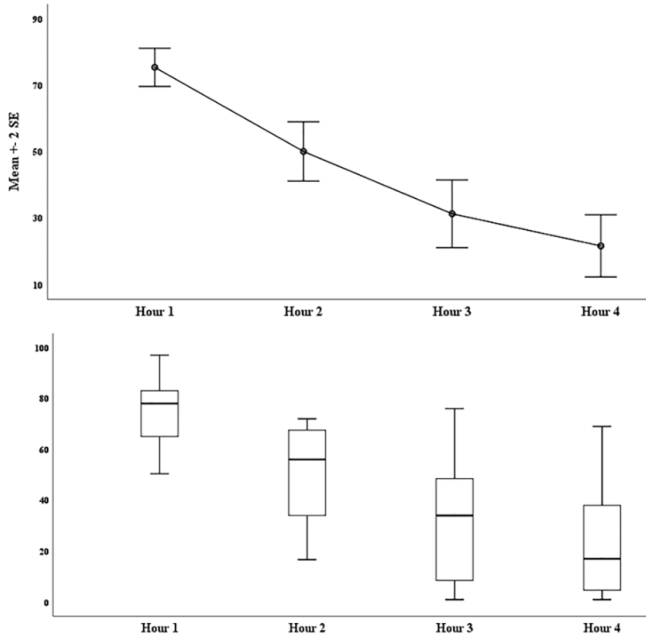

Figure 2. Error bar plot and box plot of the amount of retained activity in the stomach at various time points. The line connecting the means or medians seems to be fitted to an exponential curve

made as delayed rose to 9 (52.9%), whereas the normal was 8 (47.1%). Finally, at hour 4, the results were 10 (58.8%) as delayed and 7 (41.2%) as normal. As can be seen in Table 3, from the 2 h to 3 h time point, 4 subjects who were normal were rediagnosed as delayed and vice versa, and one subject who was delayed in hour 2 was reclassified as normal. All subjects who were labeled as delayed in hour 3 remained with the same diagnosis and 1 out of 8 subjects categorized as normal in hour 3 changed to delayed. For testing agreement, the coefficient of kappa was computed between each pair. The agreement between diagnosis in hour 2 and hours 3 or 4 was not strong (kappa <0.6 for both pairs). However, a strong agreement was found between diagnosis in hours 3 and 4 (kappa: 0.881) (Table 4).

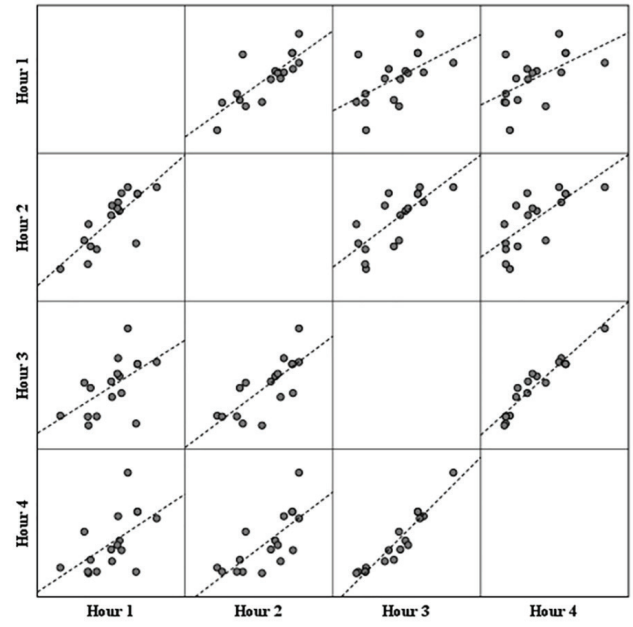

Figure 3. Matrix scatterplot of pairs at various time points. Pairs of hours 3 and 4 show the strongest correlation.

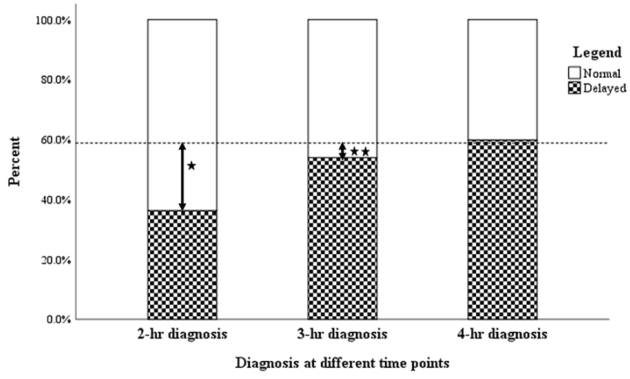

Figure 4. Stacked bar chart for diagnosis at time points of 2, 3 and 4 h. The dotted horizontal line represents the percentage of patients diagnosed as delayed (patterned part of the bar). As can be seen, the difference between hours 2 and 4 (shown by asterisk) is noticeable compared to that between hours 3 and 4 (shown by double asterisk), in which the difference is negligible

Discussion

GES as a useful tool for non-invasive evaluation of the physiology of the stomach still need to be standardized in performance of the procedure and interpretation. Several mathematical methods for measuring the emptying rate of the stomach have been proposed. Some methods derive parameters from a dynamic image continuously acquired from ingestion up to a desired time, for example, 1 or 2 h. Other methods employ static images obtained at various

Table 3. Reclassification of the diagnosis of subjects from hour 2 to hours 3 and 4 and from hour 3 to hour 4

Initial diagnosis at each time point			Reclassification of diagnosis the following time extension			
			To 3 h		To 4 h	
Time point	Diagnosis	Number (%)	Diagnosis	Number (%)	Diagnosis	Number (%)
Diagnosis at hour 2	Normal	11 (64.7%)	Normal	7 (63.6%)	Normal	7 (63.6%)
			Delayed	4 (36.4%)	Delayed	4 (36.4%)
	Delayed	6 (35.3%)	Normal	1 (16.7%)	Normal	0 (0.0%)
			Delayed	5 (83.3%)	Delayed	6 (100%)
Diagnosis at hour 3	Normal	8 (47.1%)	N/A	N/A	Normal	7 (87.5%)
			N/A	N/A	Delayed	1 (12.5%)
	Delayed	9 (52.9%)	N/A	N/A	Normal	0 (0.0%)
			N/A	N/A	Delayed	9 (100%)

N/A: Not applicable

Table 4. Results of the agreement test between diagnosis at different pairs of time points

The test of agreement between variables pairwise		Kappa coefficient	p value
2 hr diagnosis	3 hr diagnosis	0.422	0.064
	4 hr diagnosis	0.553	0.011
3 hr diagnosis	4 hr diagnosis	0.881	0.000

time points and provide parameters different from the former. Each has its own advantages and disadvantages (2,3,10,11). The method that is used more commonly in clinical settings and is recommended by consensus guidelines is imaging at 1 h intervals up to 4 h to maximize the sensitivity. Although the lag phase and emptying half-time cannon be computed, this method is sufficiently reliable and easy to perform in imaging centers. It has been shown that delayed imaging improves the diagnostic accuracy of GES and finds patients with delayed emptying whose scan up to 2 h is indicated as a normal result. However, to what extent the imaging in 4 h compared to 3 h scanning improves the diagnostic accuracy and what percentage of patients would benefit from is still under debate. In other words, it is less known how much extending the scanning up to 4 h outweighs and prevails over the one up to 3 h. In our study, correlation testing showed that consecutive time points were well correlated. Particularly, pairs of 3 and 4 h depicted an excellent correlation (r=0.951). Additionally, based on dichotomous diagnosis (normal versus delayed), a strong agreement was found between the diagnosis in hour 3 compared to hour 4. According to the results presented in Table 3, in patients whose diagnosis was normal in hour 3, 12.5% changed to delayed and likewise, in those with diagnosis labeled as delay in hour 3, none reclassified in terms of diagnosis. We think that the difference between scanning up to 3 h in comparison to 4 h adds little to the final diagnosis and may not be noticeably meaningful, especially in clinical practice. Our study results agreed with previous investigations (5,6,7,8). However, we emphasized and focused our attention on the respective difference between numerical results and diagnosis in hours 3 and 4, contrary to previous research that investigated the difference between hours 2 and 4 (5,6,7,8). Another point worth noting is that making a diagnosis based on numbers or numerical values may lead to false-positive and false-negative results. Visual interpretation to recognize the pattern ought to be used as an adjunct to quantitative analysis to maximize the accuracy of GES (12). We are aware that the number of participants in our study was, to some degree, low and this may affect the conclusion, particularly in calculating the percentages of patients with reclassification of diagnosis. An innate shortcoming of such quantitative methods and comparing the results of each time point with constant reference values may lead to discordant results with the physician's clinical suspicion and impression.

Study Limitations

One of the limitations of our study is that the clinical data of the participants were excluded from the analysis and the interpretation was only the results of scans, although the patients who were clinically suspected of gastroparesis were included. Another issue is the number of subjects enrolled in the study, which might affect the results.

Conclusion

Because of excellent correlation between values of hours 3 and 4 and strong agreement between the diagnosis in those time points, extending acquisition from 3 to 4 h

adds little to final diagnosis and may not be noticeably meaningful, especially in the clinical setting with high throughput.

Ethics

Ethics Committee Approval: Affairs-Shahid Beheshti University of Medical Sciences Ethics Committee (approval no: IR.SBMU.RETECH.REC.1402.058, date: 16.04.2023).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.Q., A.A., Design: M.Q., E.H., R.A., Data Collection or Processing: M.Q., R.A., Analysis or Interpretation: M.Q., E.H., R.A. A.A., Literature Search: E.H., R.A., Writing: M.Q., E.H., R.A. A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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