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Swallowing study using water-soluble contrast agents may increase aspiration sensitivity and antedate oral feeding without respiratory and drug complications

A STROBE-compliant prospective, observational, case-control trial

Chang Ho Hwang, MD, PhD[a,*]

Abstract

Although the modified barium swallowing study (MBSS) is considered the gold standard for assessing aspiration risk, aspiration of lipid-soluble barium can cause chemical pneumonitis or impair radiologic interpretation of the lungs. Water-soluble contrast agents (WSCAs) may avoid these complications while maintaining sensitivity on aspiration.

This prospective, observational, case-control cohort trial evaluated all patients >3 years old referred for swallowing study from September 2015 to November 2017. Repeat evaluations of individuals were excluded. High-risk patients were evaluated by WSCA (iohexol)-based swallowing study (WSS) and others by MBSS.

The study included 829 evaluations of 762 patients. After excluding 74 evaluations, 365 WSSs and 390 MBSSs were performed. The most frequent underlying condition was brain lesion, followed by aspiration pneumonia. Aspiration occurred more frequently in WSS (147 patients: 40.3%) than in MBSS (36 patients: 9.2%) (P = .00). However, neither aspiration volume (6.72 cc [3.09-10.35] vs 5.53 cc [2.21-8.85]) nor radiographic alterations differed between the 2 groups (P > .05). Moreover, the swallowed (16.62 cc [8.45-24.79]) and aspirated amounts of iohexol were not correlated with radiologic changes or deterioration (P > .05). Switching to oral feeding following WSS was more frequent (164 patients: 44.9%), whereas aspiration pneumonia was not (P = .00). WSS did not prolong the interval to patient discharge (P = .06) or induce an allergic reaction or chemotoxicity over 1 week.

The absence of aspiration-induced complications and adverse drug effects suggests that, compared with MBSS, WSS may increase aspiration sensitivity and early switching to oral feeding.

Abbreviations: CA = contrast agent; MBSS = modified barium swallowing study; WSCA = water-soluble contrast agent; WSS = WSCA-based swallowing study

Key Words: aspirations, deglutition disorder, pneumonia, rehabilitation pulmonary, solubility

1. Introduction

Aspiration pneumonia prolongs hospital stay and increases medical comorbidities and social costs. In most patients, aspiration pneumonia starts as noninfectious repetitive microaspirations. Although the most important risk factor for aspiration pneumonia is swallowing dysfunction, many patients do not present with this condition until pneumonia is established.[1] Thus, an earlier and more reliable diagnosis of swallowing dysfunction can allow earlier intervention to prevent aspiration pneumonia.

The modified barium swallowing study (MBSS) is the gold standard for assessing aspiration, with high inter-rater and intra-rater reliability.[2–4] Moreover, MBSS has high positive (85%) and negative (97%) predictive values on aspiration.[5] Barium sulfate contrast agent (CA) has been used for MBSS since the mid-1980s. However, aspiration of this agent can cause serious complications due to its lipid-solubility,[6] with mortality rates as high as 30% following massive aspiration.[7] Moreover, aspirated barium particles are phagocytosed and relocated to subpleural, centrilobar, or random areas. Small amounts of these

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[a] Department of Physical and Rehabilitation Medicine, Chungnam National University Sejong Hospital, College of Medicine, Chungnam National University, Sejong, Republic of Korea.

**Correspondence: Chang Ho Hwang, MD, PhD, Department of Physical and Rehabilitation Medicine, Chungnam National University Sejong Hospital, College of Medicine, Chungnam National University, 30099, 20, Bodeum 7-ro, Sejong, Republic of Korea (e-mail: chhwang1220@cnu.ac.kr).*

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particles can persist for up to 2 years, disturbing the interpretation of radiologic results.[8–10]

Water-soluble contrast agents (WSCAs) have been administered intravascularly to patients undergoing computed tomography or angiography.[11] One WSCA, iohexol, was approved by the US Food and Drug Administration in 1985 for gastrointestinal evaluation.[12] Nevertheless, the radio-opacity reliability of WSCAs remains unclear. Compared with barium, a WSCA showed a similar diagnostic accuracy for esophageal disruption in 11 patients.[13] However, compared with WSCSs, barium was better able to characterize leaks in 33 patients undergoing upper gastrointestinal surgery.[14] Moreover, because WSCAs are water-soluble, they can evaporate within several hours to a few days while not inducing the intense chemical reactions characteristic of barium.[7] Nonetheless, aspiration of WSCAs may result in hyperosmolarity-induced pulmonary edema.[15–18]

This study hypothesized that WSCAs had sufficient solubility in water and low osmolarity to avoid aspiration-induced chemical/hyperosmolar reactions and sufficient radio-opacity to detect aspiration. Outcomes were therefore compared in patients analyzed by MBSS and WSCA-based swallowing study (WSS).

2. Methods

A prospective, observational, case-control, cohort study was performed at a tertiary medical center/university teaching hospital on patients who underwent MBSS or WSS from September 2015 to December 2017. The study protocol was approved by the institutional review board of the Ulsan university hospital (UUH01801010) in accordance with the Declaration of the World Medical Association (www.wma.net) and was registered at www.clinicaltrials.gov (NCT03598491) and protocols.io: https://dx.doi.org/10.17504/protocols.io.bqrhmv36. Patients who were referred for swallowing study were included after providing informed written consents. In case of the participants under the age of 19 years, informed consent had been obtained from a parent or legal guardian. Children aged <3 years were excluded. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Based on their medical conditions and aspiration risk, patients undergoing the swallowing study were assigned to iohexol 350 (Omnipaque [osmolarity 541 mOsm/L, viscosity 10.4 centipoise at 37°C, specific gravity of 1.406], GE Healthcare, USA)[19] or barium sulfate ($BaSO_4$ 40% [osmolarity 233 mOsm/L, viscosity 2.3 centipoise at 25°C])[20] as the CA. Patients with a history of iodine allergy underwent MBSS. All patients were evaluated by a physiatrist with an intrarater reliability of oropharyngeal swallowing efficiency of 0.87, based on MBSS.[21] The demographic and clinical characteristics of all patients were collected, including underlying diseases, performance of tracheostomy, feeding methods, radiologic findings before and after the swallowing study, total hospital stay, and days to discharge. Results suggesting pneumonitis, pulmonary edema, allergic responses, or chemotoxicity-related laboratory/vital findings were collected over 1 week after the evaluations.[22] Radiologic change was interpreted by 6 independent radiologists.

If present, Levin tubes were removed >4 hours before the evaluations and oxygen was provided, as requested. Based on the penetration-aspiration scale, aspiration was defined as CA passing below the vocal folds.[23] Patients were asked to sit in a wheel-chair with neutral neck, erect trunk, hips, and knees flexed to 90°, and feet in contact with the floor. Patients were allowed to grip a safety bar, or assistants held their trunk, if necessary. Patients were assessed in lateral or anterior-posterior view using a fluoroscope (Shimavision 3500 HG, Shimadzu, Republic of Korea). MBSS was performed according to the modified Logemann protocol; nectar-thick liquid was first evaluated and pureed, yielding semisolid and solid test diets, and finally juice-thick liquid.[24] WSS was performed using Hwang protocol, consisting of juice-thick liquid and then pureed, semisolid, and solid diets. The amount of each material depended on the results of preceding analyses.

2.1. Statistics

Normal distribution, skewness, and kurtosis were assessed using the Shapiro-Wilk or Kolmogorov-Smirnov test, and non-normally distributed variables were log-transformed. Parameters in the MBSS and WSS groups were compared by the Chi-square test, Fisher exact test, or 2-sample independent t-tests, as appropriate. The amounts of swallowed and aspirated CA were compared with radiologic change or aggravation within each group by Spearman correlation analysis. Demographic data were analyzed by 2-sample independent t-tests or Fisher exact tests, as appropriate. All statistical analyses were performed using Statistical Package for the Social Sciences 24 software, with $P < .05$ considered statistically significant.

3. Results

The study included 829 evaluations of 762 patients. After excluding 74 evaluations, 755 evaluations were analyzed, 365 by WSS and 390 by MBSS (Fig. 1). The total volumes of iohexol and of barium provided in solution were 16.62 cc (8.45–24.79) and 11.74 cc (4.12–19.36), respectively. Each patient required about 15 minutes to complete the evaluations.

3.1. Demographic characteristics

Supratentorial and infratentorial brain lesions were the most common underlying diseases, followed by aspiration pneumonia. Poor medical condition was more frequent in patients who underwent WSS (Table 1).

3.2. Clinical features of swallowing studies with water-soluble and lipid-soluble agents

Aspirations were observed more frequently in WSS than in MBSS. Fewer than 3% of patients in each group presented with symptoms and signs suggesting pneumonitis or pulmonary edema. Although >50% of patients in both groups were maintained on their previous feeding methods after the evaluations, switching to oral feeding increased following WSS. Hospital stays were prolonged after WSS, but there was no difference in discharging days from the evaluations (Table 2).

3.3. Correlation of contrast agents with radiologic alterations after swallowing study

Of 183 patients showing aspiration during the evaluations, 116 patients after WSS and 18 after MBSS underwent radiologic reexaminations, after a mean 2.97 (1.34–4.60) and a maximum of 5 days. There were no differences between the 2 groups in swallowed and aspirated volumes of CAs ($P = .27$ and .20) (Table 3). Radiographic alterations did not differ between the 2 groups (Table 2), including the 42 patients with aspiration pneumonias, the 38 with supratentorial brain lesions, the 15 with infratentorial brain lesions, the 8 with peripheral nervous system diseases, the 5 with tongue and laryngeal cancers, the 4 with esophageal cancers, the 2 who had undergone cervical spine surgery, and the 2 with deep neck infections after WSS; and the 8 with aspiration pneumonias, the 6 with supratentorial brain lesions, the 2 with esophageal cancers, and the 2 with infratentorial brain lesions after MBSS. Moreover, the swallowed and

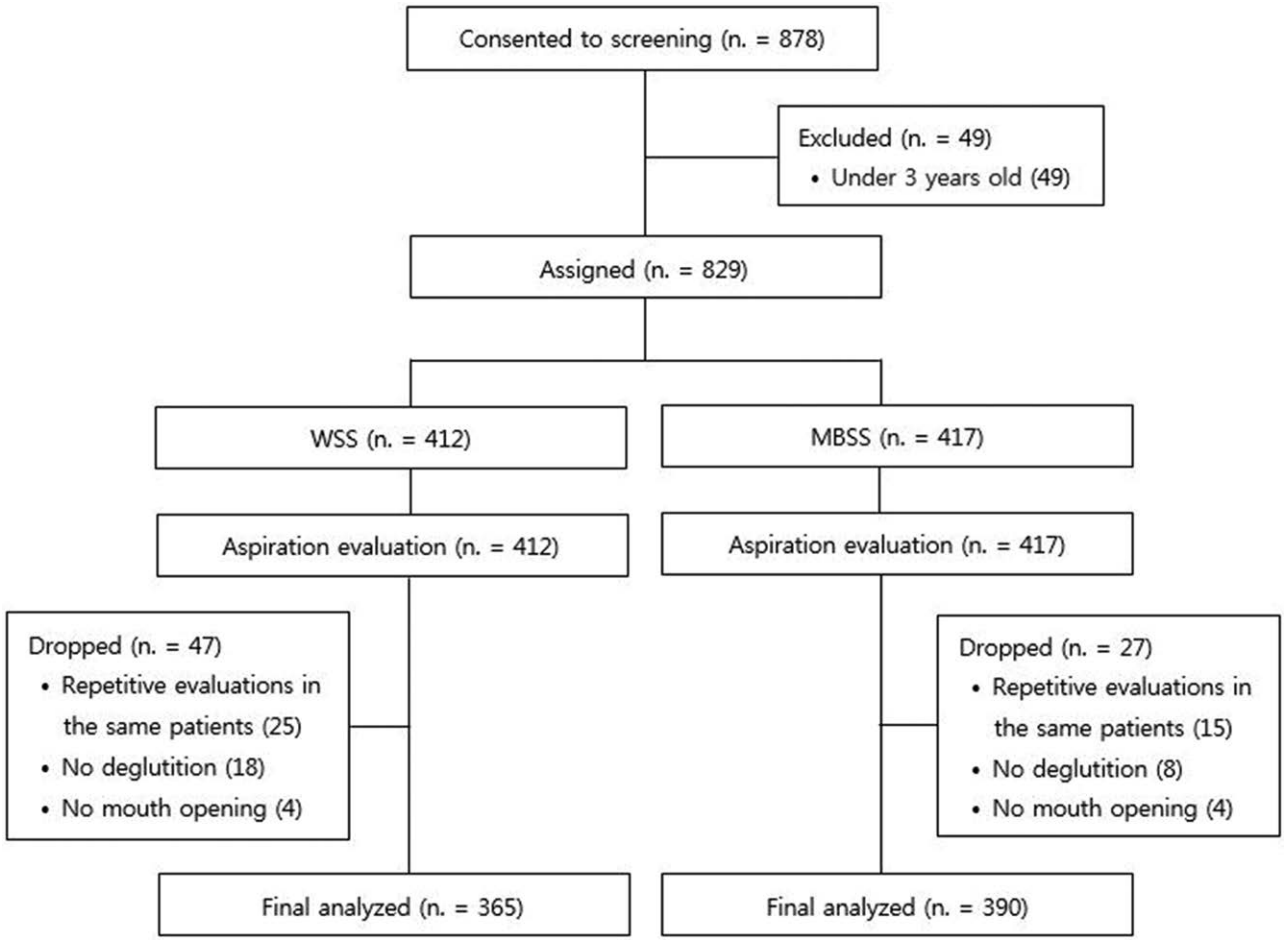

Figure 1. Flow diagram. MBSS = modified barium swallowing study, WSS = water-soluble contrast agent-based swallowing study.

Table 1

Demographic characteristics

		Iohexol (n = 365)	Barium (n = 390)	
		Number (%)	Number (%)	*P*
Sex‡	Male	240 (65.8)	244 (62.6)	
	Female	125 (34.2)	146 (37.4)	
Age (yr)†		67.6 ± 16.6	61.4 ± 17.5	0.06
Mean ± SD				
Underlying causes‡	Brain: supratentorial lesion	141 (38.6)	207 (53.0)	
	Aspiration pneumonia	100 (27.4)	32 (8.2)	
	Brain: infratentorial lesion	50 (13.7)	85 (21.8)	
	Peripheral nervous system disorder	44 (12.1)	35 (9.0)	
	Tongue and larynx cancer	13 (3.6)	7 (1.8)	0.79
	Others	8 (2.2)	10 (2.6)	
	Esophageal cancer	5 (1.4)	2 (0.5)	
	Cervical spine surgery	2 (0.5)	1 (0.3)	
	Deep neck infection	2 (0.5)	2 (0.5)	
	Thyroid cancer	0 (0.0)	9 (2.3)	
Tracheostomy‡	Yes	73 (20.0)	22 (5.6)	0.00
	No	292 (80.0)	368 (94.4)	
Oral feeding before evaluation‡	Yes	116 (31.8)	339 (86.9)	0.00
	No	249 (68.2)	51 (13.1)	

†Two sample independent t-tests.
‡Fisher exact tests.

Table 2

Clinical features of swallowing study with water-soluble and lipid-soluble agents

			Iohexol (n = 365)	Barium (n = 390)	
			n. (%)	n. (%)	*P*
Penetration-aspiration scale during evaluation*		Normal (I)	146 (40.0)	280 (71.8)	0.00
		To vocal folds (II–V)	72 (19.7)	74 (19.0)	
		Below vocal folds (VI–VIII)	147 (40.3)	36 (9.2)	
	Radiographic examination after evaluation†	Improvement	20 (13.6)	8 (22.2)	0.07
		Unchanged	88 (59.9)	8 (22.2)	
		Worse	8 (5.4)	2 (5.6)	
	No radiographic examination after evaluation		31 (21.1)	18 (50.0)	
Sx and Sg of pneumonitis†	Yes		8 (2.2)	2 (0.5)	0.06
	No		357 (97.8)	388 (99.5)	
Allergic reaction after evaluation†	Yes		0 (0.0)	0 (0.0)	0.80
	No		365 (100.0)	390 (100.0)	
Dietary change after evaluation†	No changes		187 (51.3)	342 (87.7)	0.00
	To oral feeding		164 (44.9)	39 (10.0)	
	To tube feeding		14 (3.8)	9 (2.3)	
Oral feeding after evaluation*	Yes		266 (72.9)	369 (94.6)	0.00
	No		99 (27.1)	21 (5.4)	
Total hospital stay (day)‡ Mean (CI)			48.2 (11.3-85.1)	37.7 (16.2-59.2)	0.00
Days from evaluation to discharge‡ Mean (CI)			19.5 (3.0-36.0)	14.9 (2.2-27.6)	0.06

*Chi-square tests.
†Fisher exact tests.
‡Two sample independent t-tests.
CI = confidence interval, Sg = sign, Sx = symptom.

Table 3

Correlation of contrast agents with radiologic alterations after swallowing study

		Mean (CI)	Radiologic changes (3 components) *R* (*P*)	Radiologic changes (worsening vs unchanged and improvement) *R* (*P*)
Aspiration during evaluation with iohexol (n = 147)	Swallowed iohexol, amount (cc)	16.62 (8.45-24.79)	–0.08 (0.38)	–0.02 (0.82)
	Aspirated iohexol, amount (cc)	6.72 (3.09-10.35)	0.01 (0.90)	–0.07 (0.46)
Aspiration during evaluation with barium (n = 36)	Swallowed barium, amount (cc)	11.74 (4.12-19.36)	–0.04 (0.65)	–0.02 (0.92)
	Aspirated barium, amount (cc)	5.53 (2.21-8.85)	0.01 (0.79)	–0.04 (0.65)

2-sample independent t-tests or Spearman correlation analysis.
CI = confidence interval.

aspirated amounts of iohexol did not correlate with radiologic changes or deterioration (Table 3).

3.4. Adverse effects

None of the patients experienced immediate or delayed allergic responses or chemo-toxicities within 1 week after the evaluations (Table 2).

4. Discussion

The validity of WSCA was assessed in 762 patients over 28 months to determine whether the reliability of aspiration detection was maintained and to avoid respiratory complications associated with barium. The key findings were that (1) WSS was significantly better at detecting aspiration than MBSS; (2) aspirated WSCS was not accompanied by significant pulmonary edema, whereas chemical pneumonitis resulted from aspirated barium; (3) oral feeding increased following WSS, but aspiration pneumonia did not; (4) hospital stay after WSS was not prolonged; and (5) WSS was not associated with allergic reactions or chemotoxicity.

In the current trial, WSS had significantly greater sensitivity in diagnosing aspiration than did MBSS, with rates of aspiration of 40.3% and 9.2%, respectively. These findings suggested that WSCAs may be superior to barium in detecting aspiration in the upper respiratory tract. However, 4 phantom experiments using 19-cm thick plexiglas found that the high iodine-containing diatrizoate showed inferior visibility to barium.[25] Other WSCAs with lower iodine levels have lower radiodensities than diatrizoate, with limited detection of leakage into the gastrointestinal tract.[14,26] Nonetheless, iopamidol 370 had good diagnostic visibility on bronchoscopy in 50 rats, contrary to iopamidol 150, which showed poor diagnostic quality. Hence, radiodiagnostic ability may depend on iodine concentration.[17] Because iohexol 370 with the same iodine strength as iopamidol 370[22] showed significant sensitivity of aspiration in the current trial, iohexol 370 may have sufficient radio-opacity to detect aspiration in the upper respiratory tract, as well as in the gastrointestinal tract.

Aspiration was more frequent in the WSS than in the MBSS group (40.3% vs 9.2%), whereas penetration was similar (19.7% vs 19.0%) in these groups. Previously, aspiration was observed in 8% of 36 patients with WSCA and in 47% of 206 patients with barium.[8] That trial, however, was cross-sectional in design and included patients that differed in disease,

operations, invasive procedure, radiotherapy, or head and neck trauma. Moreover, it concerned leakage into the gastrointestinal tract, with most aspirations >5 cc caused by fistulae. Most brain lesions in the WSS (52.3%) and MBSS (74.9%) groups were strokes. Dysphagia is so common (35% of 406 patients) in acute stroke patients[27] that the 2 trials could not be compared. Moreover, a thin liquid with the consistency of juice had a higher risk of aspiration than other test materials,[5] such that it is evaluated at the end of the experiment due to the possibility of chemical pneumonitis in patients undergoing MBSS.[24] Because the thin liquid was first examined during WSS, physicians knew the aspiration risks from the initial stage of WSS. Because WSCAs are water-soluble and do not induce chemical reactions,[7,8] physicians have greater freedom to increase the volume when using a WSCA.[7] Aspiration is likely to increase as the volume of materials increases,[28] resulting in WSS having greater sensitivity than MBSS. Because nonplugged tracheostomy decreases subglottic pressure, it can increase aspiration.[29] Indeed, WSS was increased in tracheostomy patients in the current trial.

Of the 147 patients who experienced aspiration after WSS, 116 underwent radiologic reevaluation and 8 (5.4%) presented with radiologic worsening. Of the 36 patients who experienced aspiration after MBSS, 18 were reevaluated and 2 (5.6%) showed radiologic aggravation. In comparison, of 53 patients with iohexol entering into the airways, only 3 (5.6%) experienced pulmonary edema.[8] Radiologic evaluation showed that the prevalence of pulmonary edema was nearly the same in the 2 trials. Because 0.15 cc of iohexol (equivalent to a volume of 8.4 cc in adults weighing 80 kg) fully induced pulmonary edema in adult rats, the mean aspirated volume (6.72 cc [3.09-10.35]) may be sufficient to determine whether iohexol induces pulmonary edema. However, the only radiologic changes without clinical manifestations were pneumonitis-related presentations, observed in 8 patients after WSS. Moreover, aspirated volume did not correlate significantly with radiologic alterations. WSCAs of high osmolarity can induce the leakage of interstitial fluid into parenchymal tissue,[15] whereas lower osmolarity WSCAs may be associated with reduced pulmonary edema.[16] However, WSCA properties, including type and osmolarity, responsible for pulmonary edema remain unclear, with histologic reactions not differing among iso-osmolar iotrolan 300, hyperosmolar iopamidol 370, and normal saline on day 8, and the reaction to iopamidol 370 being lower than that to normal saline in 60 rats.[17] In addition, there were no significant differences in histology between iso-osmolar iodixanol 270 and hyperosmolar iohexol 270, with the reaction induced by iodixanol being lower than the reaction induced by normal saline in 30 rabbits.[16] Furthermore, rates of alveolar hemorrhage were higher in 24 rats treated with iohexol 300 (672 mOsm/L) than with saline and diatrizoate (1940 mOsm/L).[18] Compared with barium, iohexol 350 (10.4 centipoise at 37°C) did not significantly enhance the rate of osmolarity-induced injury in the current trial. Similarly, the spread of iopamidol 370 into tissues was less than that of normal saline, a finding that may be related to the higher viscosity of the former than the latter (9.4 vs 1 centipoise at 37°C).[17] Additionally, the ability of WSCAs to vaporize within a few hours to 2 days may have affected the results.[8]

In the current trial, switching to oral feeding increased following WSS. Increased sensitivity on aspiration meant a reduced false negative rate, enabling physicians to start oral feeding. Following WSS, 164 patients (44.9%) newly started oral feeding, compared with 39 patients (10%) after MBSS. Following oral feedings, there were such no significant between group differences in radiologic alterations or pneumonitis-related presentations over 1 week, suggesting that oral feeding trials based on WSS may not increase aspiration pneumonia rates. However, 86.9% of patients in the MBSS group maintained oral feeding, suggesting a ceiling effect. Additionally, oral feeding included modified diets as well as regular diets. Total hospital stay was more prolonged in the WSS than in the MBSS group, a finding that may be due to the higher rate of medical situations like tracheostomy and tube feeding in the WSS group. Moreover, out-patient ratio was not balanced (18 in the WSS and 39 in the MBSS group). Interestingly, there was no difference in discharge days after the evaluations.

None of the 365 patients who ingested WSCS experienced immediate or delayed allergic reactions or dose-dependent chemotoxicity. In previous studies, by contrast, 7 (7%) of 101 patients experienced one or more adverse effects following iohexol injection,[22] as did 172 (11.3%) of 1514 patients who received WSCA injections.[30] These findings suggest that oral provision is safer than intravascular administration. A controlled clinical trial of 54 adults who swallowed iohexol for gastrointestinal tract evaluation found that 23 (42%) complained of >1 adverse event, such as diarrhea or abdominal pain, although that study did not report concentration or volume of iodine.[31] Another study reported that 1 (1.8%) of 53 patients experienced brief stridor, with iohexol entering into the airways.[8] These findings suggest that orally administered WSCSs may induce rare adverse reactions. In the current study and the trial of Harris et al, however, barium was administered to patients with a history of iodine allergy.

This study had several limitations, including its observational, cohort design with no sham controls. Selection bias may have arisen because high-risk patients were evaluated with WSCS and repeat evaluations in individual patients were excluded. Because only patients with clinical suspicion were radiologically re-examined, all patients showing aspiration as well as all enrolled patients were not re-examined. Moreover, half the patients in the MBSS group did not undergo radiologic reevaluation. Although analyses should also include the aspirated amounts of CAs that were mixed with other test diets as well as that in solution, this study was limited to differentiating CAs from total test materials using radiologic images. In assessing aspiration-induced alveolar reaction, it may not have been appropriate that differentiation between pulmonary edema and chemical pneumonitis was based on radiologic changes or clinical manifestations, not on histologic evaluation. Because 2-phased foods have higher risk of aspiration than single-phase foods,[32] the current results may not represent practical diets. Moreover, assessments of cost-benefit ratios should compare the extra costs of WSCAs (40–100 US dollars) with the social costs of aspiration pneumonia.

5. Conclusions

WSCA-based swallowing study may be more sensitive and more antedating of oral feeding than classic MBSS in adult patients. WSCA may not increase the risks of pulmonary edema, aspiration pneumonia, or adverse effects. Additional trials are needed to determine WSCA are preference, as determined by osmolarity, iodine concentration, and radio-opacity. However, selection bias and nonrandomization occurred during the participant assignment, indicating that the current study might only be useful to determine the feasibility of the suggested technique, and it is still unclear whether the positive findings were due to lack of statistical power or some underlying scientific principle.

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Author contributions

Chang Ho Hwang: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing—original draft, writing—review and editing.

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