Effect of Different Iodine Concentrations on Patient-Reported Discomfort in Contrast-Enhanced Computed Tomography: A Prospective Comparative Trial

Effekt verschiedener Jodkonzentrationen auf patientenberichtete Missempfindungen während kontrastmittelverstärkter Computertomografie: Eine prospektive Vergleichsstudie

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ZUSAMMENFASSUNG

Ziele Die Reduktion der Injektionsgeschwindigkeit von jodhaltigen Kontrastmitteln kann kontrastmittelassoziierte Missempfindungen während CT-Untersuchungen reduzieren. Um eine exzellente Kontrastierung der Bilder zu garantieren, erfordert dieser Ansatz höher konzentrierte Kontrastmittel. Ob hochkonzentrierte Kontrastmittel die Patientenwahrnehmung während der CT-Untersuchung beeinflussen, ist bislang unzureichend untersucht. Das Ziel der vorliegenden Studie war es zu untersuchen, ob verschiedene Konzentrationen von intravenös verabreichtem, jodhaltigem Kontrastmittel einen Einfluss auf patientenberichtete Missempfindungen während der Untersuchung haben.

Material und Methoden Patienten wurde in 2 Gruppen randomisiert und erhielten entweder Iomeprol 400 mg/ml (Gruppe A) oder Iomeprol 300 mg/ml (Gruppe B) während Routine-CT-Untersuchungen. Jodinjektionsrate und Injektionszeit waren in beiden Gruppen gleich. Nach der Kontrastmittelgestützten CT-Untersuchung beantworteten die Studienpatienten Fragen zu verschiedenen Kontrastmittelassoziierten Missempfindungen mittels digitalen, visuellen Analogskalen (VAS).

Ergebnisse Innerhalb von 6 Monaten konnten 253 konsekutive Patienten eingeschlossen werden. In beiden Studiengruppen berichtete die Mehrheit der Patienten Wärme-Missempfindungen (Mittelwert VAS: 5,3 mm bei Gruppe A vs. 5,0 mm bei Gruppe B; $p = 0,5$). Geschmackssensationen traten ebenso ohne signifikanten Unterschied in beiden Gruppen auf (2,4 mm vs. 2,0 mm; $p = 0,08$). Schmerzempfindungen traten signifikant geringer bei Studiengruppe B auf (1,3 mm vs. 1,0 mm; $p = 0,005$), obwohl Schmerzen während der Injektion bei beiden Studiengruppen auf sehr geringem Niveau berichtet wurden. Andere Kontrastmittelassoziierte Missempfindungen wurden sehr selten angegeben.

Schlussfolgerungen Patientenberichtete Missempfindungen waren in beiden Studiengruppen (Iomeprol 400 mg/ml vs. 300 mg/ml) auf einem sehr geringen Niveau und unterschieden sich nur geringfügig zwischen beiden Studiengruppen. Die Injektion von höherkonzentriertem Kontrastmittel zeigte eine vergleichbare Patientenakzeptanz, was eine Reduktion der Injektionsgeschwindigkeit und des Injektionsvolumens während CT-Untersuchungen erlaubt.

Kernaussagen:

- Patientenberichtete Missempfindungen waren in dieser Studie auf einem sehr geringen Niveau.
- Das höherkonzentrierte Kontrastmittel (HKKM) zeigte im Vergleich eine analog hohe Patientenakzeptanz.
- HKKM erlauben geringere Injektionsraten bei gleichbleibender Jod-Flussrate.

ABSTRACT

Purpose Reducing contrast media injection speed while maintaining iodine flux is a promising workaround to lower or avoid contrast media-related discomfort during CT examinations. This approach demands contrast media with a higher concentration to guarantee excellent image quality. It remains unclear whether these concentration changes affect the patient's experience. Thus, the aim of this study was to evaluate the influence of different concentrations of intravenous iodinated contrast media on patient discomfort during and after contrast media delivery.

Materials and Methods Patients were randomized to receive either iomeprol 400 mg/ml (group A) or 300 mg/ml (group B) during routinely scheduled CT examinations at our department. The iodine delivery rate and injection time were kept constant in both groups. After examination, study subjects completed a digital questionnaire on different CM-related sensation items using digital visual analogue scales.

Results 253 consecutive patients were enrolled in a 6-month period. Most of the patients reported heat sensation in both groups (mean VAS: 5.3 mm in group A vs. 5.0 mm in group B, $p = 0.5$). Taste sensation also did not differ significantly between both groups (2.4 mm vs. 2.0 mm, $p = 0.08$). Pain sensation was reported to be significantly lower in group B

patients (1.3 mm vs. 1.0 mm, $p = 0.005$), even though pain sensation in general was reported on a very low level. Other injection-related sensations were rarely reported.

Conclusion Patient-reported discomfort during intravenous injection of high-concentration contrast media (400 mg/ml) was low and only marginally different when compared to the injection of contrast media with a lower concentration. The injection of highly concentrated contrast media showed comparable overall patient acceptance, allowing a reduction of the injection speed and volume during examinations.

Key Points:

- Patient-reported, contrast-related discomfort was very low in this study.
- High-concentration contrast media (HCCM) showed comparable overall patient acceptance.
- HCCM allow a reduction of injection speeds while keeping iodine flux constant.

Citation Format

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Introduction

The introduction of computed tomography (CT) in the 1970s has led to epochal achievements in medical imaging. Nowadays, it is a day-to-day tool for the noninvasive diagnosis of numerous diseases. Reliable CT depends greatly on the use of intravenous, iodinated contrast media (CM). Different types of iodinated CM are available. High to low concentrations of iodine allow the injection of different CM volumes [1].

CM injection-related discomfort and adverse reactions (ADR) have been a well-known problem since the 1980s but have decreased [2–4]. Modern non-ionic contrast media are reported to be safe [1]. Besides adverse effects, CM injection is often accompanied by patient discomfort including heat, taste and pain sensations [5–7]. A cold sensation, nausea, pruritus and the desire to urinate are rarely reported. Risk factors and significance of these CM-related sensations remain unclear [8]. Adverse reactions and sensations may be correlated with the iodine concentration of the CM, the injected volume, the injection rate or the site of the injection [9–13].

Reducing the CM injection speed is suggested as a promising workaround to lower or avoid CM-related discomfort during CT examinations [14]. In order to guarantee excellent image quality, this approach demands a high iodine concentration of the CM to keep the iodine flux (delivered iodine amount per time, iodine flux F [mg/s] = c_0 [mg iodine/ml] * v [ml/s]) constant.

The purpose of the current study was to evaluate the influence of different concentrations of intravenous CM on patient-reported discomfort during and after CM delivery.

Materials and Methods

Study Design

The study was designed as a single-center pilot study. It was a prospective, observational, non-interventional, comparative trial that was conducted at a maximum-care hospital in Germany. The trial was conducted in full conformance with the Declaration of Helsinki and was approved by our institutional review board/local ethics committee. All patients gave informed consent.

During the study period, all patients in our department that were scheduled for diagnostic, routine contrast-enhanced computed tomography (CECT) were asked to participate in this study. Upon consent, patients answered a dedicated digital questionnaire immediately after their examination in order to assess contrast media-related sensations and discomfort.

To evaluate the influence of different concentrations of intravenous contrast media (CM) on patient discomfort during and after CM delivery, participating patients were randomized into two groups. During the first study period, all consecutive patients were examined using iomeprol 400 mg/ml intravenously (group A). Thereafter, all consecutive patients received iomeprol 300 mg/ml during CECT (group B) [both: Imeron®, Bracco Imaging Deutschland GmbH, Germany]. This approach ensured a certain level of randomization of patients. In both study groups, standardized CM injection protocols were chosen based on indication and referral diagnosis (i. e., tumor screening, tumor staging, aortic aneurysm). While keeping contrast timing, iodine flux and overall iodine amount constant in both study groups, the use of

► **Table 1** Two exemplary contrast media injection protocols used in this study.

► **Tab. 1** Zwei exemplarische, in dieser Studie verwendete Kontrastmittel-Injektionsprotokolle.

contrast media protocol	lomeprol 400 mg/ml (group A)	lomeprol 300 mg/ml (group B)
aortic aneurysm		
▪ injection speed	4.0 ml/s	5.3 ml/s
▪ injected volume	100 ml	133 ml
▪ iodine flux	1600 mg/s	1590 mg/s
▪ iodine amount	40 000 mg	39 900 mg
▪ injection time	25.0 s	25.1 s
tumor staging		
▪ injection speed	2.5 ml/s	3.3 ml/s
▪ injected volume	100 ml	133 ml
▪ iodine flux	1000 mg/s	990 mg/s
▪ iodine amount	40 000 mg	39 900 mg
▪ injection time	40.0 s	40.0 s

differently iodinated CM (300 mg/ml vs. 400 mg/ml) enabled us to vary the injection flow and injected volume between the two groups. This resulted in a group with relatively low injection speeds (group A) compared to the higher injection speeds applied in group B subjects with constant iodine flux in both groups.

► **Table 1** shows different exemplary injection protocols for both study groups. Every study subject was examined in the same examination room with the same 80-slice MDCT scanner (Aquilion PRIME, Canon Medical Systems, Otawara, Japan). Intravenous CM injection was performed via a 20-gauge venous access system using an Accutron CT-D injection system (Medtron AG, Germany) followed by a bolus of 40 ml of saline as a chaser.

Digital Questionnaire

We developed a dedicated questionnaire application using Xcode 6.3 build 6D570 and iOS software development kit 8.3 build 12F69 (Apple Inc., 1 Infinite Loop, Cupertino, CA 95014, USA). The application was installed on two tablet computers (iPad Air2, iOS 8.3, Apple Inc.) that were wall-mounted in the CT waiting areas. Study patients were able to initiate a new questionnaire by scanning their personal QR code with the device's internal camera. The dedicated application guided patients through 8 digital sheets with a total of 12 questions. The data entered by the patient was encrypted and stored in a local database on the device. After study completion, all patient-generated data was exported to a CSV file and imported into SPSS (IBM Corp., Version 22.0., USA).

Since there are no standardized and validated assessment tools for measuring patient experience during CM injection, we developed our own questionnaire. To ensure correct study design, independent psychologists approved the validity of the dedicated questionnaire used in this study.

Immediately after CECT acquisition was completed, every study subject was asked to answer the digital questionnaire about CM-related discomfort using one of the iPads. This approach was intended to ensure high participation rates and good reliability as well as high completion rates. Data acquisition was completely anonymized. Therefore, all patients received a personal study ID encoded in a printed QR code. Medical technical assistants recorded patient-specific CM injection parameters on a dedicated paper card on which the corresponding study ID was also printed encoded in a QR code for subsequent data entry of injection details. Discomfort and sensations were recorded using a digital visual analogue scale (VAS) of 100 mm. All VAS-assessed questionnaire items are specified in ► **Table 2**.

Analysis

SPSS was used for data analysis (IBM Corp.). Descriptive statistical analysis included the calculation of absolute and relative frequencies, mean values and corresponding standard deviations (SD). Group differences were identified by applying the student's t-test for parametric data or applying the Mann-Whitney test for ordinal data. The difference in frequencies between the study groups was analyzed by applying the Fisher's exact test. The significance level was set to 0.05 or less.

Results

We tested the patient's subjective discomfort in relation to different concentrations of intravenous CM during routine computed tomography examinations in 253 consecutive patients. All patients completed the digital questionnaire immediately after their examination. 128 patients received lomeprol with a concentration of 400 mg/ml (group A, lower injection speeds), 125 patients lomeprol with a concentration of 300 mg/ml (group B, higher injection speeds).

► **Table 3** shows the baseline characteristics and demographic data. ► **Table 4** summarizes the CM injection parameters for both study groups. As intended by study design, the flow rate and injected volume differed significantly between both study arms. As expected, no significant differences in iodine flux, delivered iodine amount and injection time were observed.

Contrast Media-Related Sensations

In general, all of the study subjects tolerated the CM injection well in both study groups. Heat sensation was the most frequently reported sensation (N = 244, 96.4 % of cases), followed by taste (N = 177, 70.0 %) and pain sensation (N = 140, 55.3 %). ► **Table 5** summarizes the VAS-assessed discomfort and sensation questions for the whole study population. No contrast media extravasation occurred in all patients. An absence of pain sensation

► **Table 2** Detailed specifications of the VAS-assessed questionnaire items used in this study.► **Tab. 2** Detaillierte Beschreibung der mittels visueller Analogskala erhobenen Fragen dieser Studie.

questionnaire item	short descriptor	type	label at 0 mm	label at 100 mm
how would you describe the contrast injection?	general experience	mandatory	completely unproblematic	extremely uncomfortable
to what extent did you experience a feeling of warmth during contrast injection?	heat sensation	mandatory	no heat sensation	extremely strong heat sensation
to what extent did you experience an unpleasant taste during contrast injection?	taste sensation	mandatory	no unpleasant taste	extremely bad taste
how much pain did you feel during the injection?	pain sensation	mandatory	no pain	extreme pain
to what extent did you feel a cold sensation during contrast injection?	cold sensation	optional	very slight	extreme
how much nausea did you feel during the injection?	nausea	optional	very slight	extreme
how much itching did you feel during the injection?	pruritus	optional	very slight	extreme
how much urinary urgency did you feel during the injection?	feeling of the need to urinate	optional	very slight	extreme
what is your attitude towards future CT examinations with CM injection?	–	mandatory	was okay, I would undergo again	I would never undergo again

► **Table 3** Baseline characteristics and demographic data (N = 253).► **Tab. 3** Basischarakteristika und demografische Daten der Studie (N = 253).

	lomeprol 400 mg/ml	lomeprol 300 mg/ml	total
completed questionnaires (%)	125 (49.4)	128 (50.6)	253 (100)
male gender (%)	76 (60.8)	68 (53.1)	144 (57)
mean response time in seconds (SD)	104 (41)	107 (47)	105 (44)
outpatients (%)	69 (55.2)	65 (50.8)	134 (53)

during contrast delivery was reported statistically more frequently in group B patients (lomeprol 300 mg/ml, ► **Table 6**).

Other Contrast Media-Related Sensations

38 patients (15.0%) reported other CM-related sensations, 20 subjects of group A (lomeprol 400 mg/ml) and 18 of group B (lomeprol 300 mg/ml). In these subgroups, the feeling of the need to urinate was the most frequently mentioned sensation (N = 12 in group A vs. N = 18 in group B). Cold sensation (N = 6 vs. N = 2), nausea (N = 5 vs. N = 2) and pruritus (N = 0 vs. N = 1) were less frequently mentioned sensations. ► **Table 7** summarizes the quantification of these other reported sensations assessed by VAS.

► **Table 4** Mean (standard deviation) of contrast media injection parameters for the lower flow group (lomeprol 400 mg/ml, N = 125) and the higher flow group (lomeprol 300 mg/ml, N = 128).► **Tab. 4** Mittelwerte und Standardabweichungen der verwendeten Kontrastmittel-Injektionsparameter getrennt nach Studiengruppen (N = 253).

	lomeprol 400 mg/ml	lomeprol 300 mg/ml	p-value ¹
flow rate ml/s	3.0 (0.7)	4.0 (0.9)	<0.001 ²
volume ml	88.4 (17.0)	116.6 (22.4)	<0.001 ²
iodine amount mg	35 360 (6785)	34 978 (6729)	0.65
injection time s	31.1 (9.3)	30.5 (8.1)	0.59
iodine flux mg/s	1201.6 (276.5)	1192.5 (261.8)	0.78

¹ Student's t-test.
t-Test.

² statistically significant.
statistisch signifikant.

Attitude Towards Future CM Injections

The last question asked the study patients about their opinion towards future CECT examinations. The average VAS values for this question were very low in both study groups, although a large variation was evident in the whole study population. The mean ($\pm$ SD) VAS value was 1.2 ($\pm$ 1.5) in group A patients (lomeprol 400 mg/ml) and 0.8 ($\pm$ 1.3) in the group B subjects (lomeprol

► **Table 5** Mean values of general experience, heat, pain and taste sensations evaluated by visual analogue scale in both study arms (N = 253).

► **Tab. 5** Mittelwerte der mittels visueller Analogskala erfassten Endpunkte generelle Erfahrung, Wärme-, Schmerz- und Geschmacks-Missempfindungen in beiden Studiengruppen (N = 253).

VAS	study arm	n	mean (mm)	SD (mm)	p-value ¹
general experience	lomeprol 400	125	2.1	2.0	0.003 ²
	lomeprol 300	128	1.6	2.1	
heat sensation	lomeprol 400	125	5.3	2.3	0.495
	lomeprol 300	128	5.0	2.8	
pain sensation	lomeprol 400	125	1.3	1.6	0.005 ²
	lomeprol 300	128	1.0	2.0	
taste sensation	lomeprol 400	125	2.4	2.6	0.079
	lomeprol 300	128	2.0	2.5	

¹ Mann-Whitney test.
Mann-Whitney-Test.

² statistically significant.
statistisch signifikant.

► **Table 6** Absence of CM-related sensations of heat, pain and taste in both study groups (N = 253).

► **Tab. 6** Fehlen von den Kontrastmittel-assoziierten Missempfindungen Wärmegefühl, Schmerz und Geschmackssensation in beiden Studiengruppen (N = 253).

	arm	n	%	p-value ¹
no heat sensation	lomeprol 400	2/125	1.6	0.172
	lomeprol 300	7/128	5.5	
no pain sensation	lomeprol 400	44/125	35.2	0.004
	lomeprol 300	69/128	53.9	
no taste sensation	lomeprol 400	32/125	25.6	0.134
	lomeprol 300	44/128	34.4	

¹ Fisher's exact test.
exakter Test nach Fisher.

► **Table 7** Mean values of urinary urgency, cold sensation, nausea and pruritus evaluated by visual analogue scale in both study arms.

► **Tab. 7** Mittelwerte der mittels visueller Analogskala erfassten Missempfindungen Gefühl des Einnässens, Kälte, Übelkeit und Juckreiz in beiden Studiengruppen.

VAS	arm	n	mean (mm)	SD (mm)
urinary urgency	lomeprol 400	18	5.1	2.5
	lomeprol 300	12	5.6	3.1
cold sensation	lomeprol 400	6	5.0	3.6
	lomeprol 300	2	3.5	0.5
nausea	lomeprol 400	5	6.5	1.9
	lomeprol 300	2	3.6	5.1
pruritus	lomeprol 400	1	6.0	–
	lomeprol 300	0	–	–

300 mg/ml). This slight difference between both study groups was not statistically significant ($p = 0.057$).

Discussion

The presented pilot study provides an analysis of the patient's subjective experience during standardized CT contrast administration at different iodine levels of 300 and 400 mg/ml while keeping the iodine delivery rate and injection time constant in both study groups. This enabled us to significantly reduce the injection rate in the 400 mg/ml study group.

While many studies focus on acute and late adverse reactions [15–17], this study evaluates the patient's experience as the main item of acceptance. We observed only minor differences in the

patient-reported, contrast-injection-related sensations of heat, taste and pain between both of our study groups (300 mg/ml vs. 400 mg/ml). All of these reported sensations were always slightly lower in the 300 mg/ml group. Heat and taste sensation did not differ significantly between the two groups. The reported pain sensation during contrast delivery was significantly lower in the 300 mg/ml group, although the difference in absolute values was only minor (mean VAS value 1.0 vs. 1.3) and on a very low level. Furthermore, the proportion of patients that reported no pain sensation at all was significantly lower in the 300 mg/ml group (35.2 % vs. 53.9 %). These pain-related group distinctions probably accounted for a significantly better general perception of contrast injection in the 300 mg/ml study group, even though the difference in the mean VAS values was only moderate (1.6 vs. 2.1). We observed a slight but not statistically significant difference when

asking patients about their attitude to repeat computed tomography with contrast administration. This slight difference in favor of the lower concentrated contrast agent might indicate a certain trend if evaluated in a larger population. Nevertheless, this difference was on a very low level indicating the overall high acceptance of contrast injection.

We did not encounter any moderate or severe adverse drug reactions (ADR) as defined in the ESUR guidelines [18]. Although warmth is defined as a mild chemotoxic acute reaction, the recent publications in this field excluded heat/warmth sensations from ADR [14, 19]. In our study, the majority of patients (96.4%) reported a feeling of heat as the main sensation, which is in accordance with other prior studies [20]. In line with previous studies, other injection-related sensations were rarely reported in our study [5, 7].

We used a dedicated digital questionnaire presented on tablet computers for data collection. Most of our study subjects appreciated this approach. Patient-reported digital data assessments offer several benefits since acquisition is fast, convenient, reliable and can help reduce the problem of missing data [21, 22]. A recent meta-analysis proved that paper-based and electronic assessment tools are equivalent with regard to measuring patient-reported data [23].

This study has some limitations. First, the en bloc recruitment and randomization of patients to both study groups could be a substantial selection bias since several studies have shown seasonal dependency of contrast-related sensations [24]. Informed consent may represent another bias of this study since study subjects were educated about possibly occurring sensations prior to their examination. Thus, the reported VAS values for the assessed sensations may be overestimated because study patients were aware of possible sensations that they might have not recognized without prior education. Furthermore, some of the elderly patients needed help using the electronic questionnaire. These cases received technical assistance, which might have influenced the precision of the values on the digital VAS. As both study groups received this kind of assistance, this possible bias might have affected both groups to the same extent.

Another limitation is the relatively small sample size of 253 cases which may limit the power to draw conclusions regarding the investigated endpoints. Age and gender probably significantly influence patient-reported, contrast agent-related discomfort [20]. Unfortunately, we were not able to perform matching of patients for these parameters from our data. Future studies on patient-reported discomfort should include a matched pairs analysis for both parameters in order to obtain more reliable results on group differences. Furthermore, we adjusted injection speed and injection volume to keep the iodine flux and amount constant between both study groups. This might have biased our results since injection speed as well as injection volume both are known to have an influence on patient-related discomfort during contrast media injection [9–12].

In conclusion, patient-reported discomfort during the intravenous injection of highly concentrated contrast media (400 mg/ml) was low in this pilot study and was only marginally different compared with the injection of lower-concentration contrast media (300 mg/ml) when adapting the application rate and injection vol-

ume. The injection of highly concentrated contrast media showed high patient acceptance allowing a significant reduction of the CM injection flow and volume without affecting contrast behavior.

CLINICAL RELEVANCE OF THIS STUDY

- Slower injection rates of iodinated contrast media could reduce contrast media-related discomfort during CT examinations.
- Highly concentrated contrast agents allow for a reduction of injection speed and injection volume and guarantee constantly high image quality.
- The injection of high-concentration contrast media showed high overall patient acceptance in this study.

Conflict of Interest

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