European Journal of Radiology 164 (2023) 110853

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Shortage of iodinated contrast media: Status and possible chances – A systematic review

David R. Koeppel, Ingrid B. Boehm *

Department of Diagnostic, Interventional, and Pediatric Radiology, University Hospital of Bern, Inselspital, University of Bern, Bern, Switzerland

ARTICLE INFO

Keywords:
Iodinated contrast medium
Low-dose contrast-enhanced image-guided examination
Shortage
Contrast-induced acute kidney injury (CI-AKI)
Hypersensitivity reactions
Breastfeeding women

ABSTRACT

Purpose: Covid-19 related lockdowns have resulted in a shortage of iodinated contrast media (ICM) in 2022. Health care providers have reacted with implementing conservation strategies to stay operational without compromising patient care. Although articles describing the implemented Interventions have been published, possible chances of the shortage have not yet been mentioned in the literature.

Methods: We conducted a literature search in PubMed and Google Scholar, and analysed the background, interventions, and possible benefits of low-dose ICM regimens.

Results: We included 22 articles dealing with "ICM shortage" for the analysis. The delivery bottlenecks in the USA and Australia led to two different countermeasures, 1. reduction of the number of contrast-enhanced image-guided examinations and 2. reduction of the (single) ICM dose. Interventions from both groups have resulted in significant reduction of ICM usage; however, group 1 has contributed more to overall ICM reduction. As benefit of the ICM reduction, we revealed an increased safety for patients at risk (e.g. hypersensitivity reactions, contrast-induced acute kidney injury, thyroid toxic effects).

Conclusion: The ICM shortage of 2022 has forced health care providers to implement conservation strategies to stay operational. Although there were already proposals for dose reduction before the corona pandemic and the associated supply bottlenecks, this situation led to the use of a reduced amount of contrast agent on a large scale. This presents a good opportunity to reconsider protocols and the use of contrast-enhanced imaging in general for future practice as it offers chances and advantages regarding costs, environmental impact, and patient safety.

1. Introduction

Currently, iodinated contrast media (ICMs) are the most common applied drugs. A broad range of different contrast-enhanced examinations in radiology (e.g. computed tomography, angiography) as well as in cardiology, gastrointestinal and vascular surgery and urology are performed with ICMs. Moreover, the number of radiological examinations is continuing to rise [1]. It is estimated that the amount of contrast enhanced CT examinations in the United States of America is approximately 120 million doses each year [2]; worldwide several 100 million doses are applied every year [3].

Due to their important role, it is clear, that a shortage of ICMs is a problematic scenario. Early in 2022, the first paper dealing with a shortage of iohexol was published [4]. Iohexol is a non-ionic monomer and makes up 50% of the ICM market in the USA and more than 75% of the market in Australia [5,6]. During the following months, the problem continued to exist, and several other papers on the shortage were published [5,7,8].

While the current ICM shortage causes challenges for healthcare-providers around the world, it also offers an opportunity to reconsider usage of ICM in diagnostic as well as in interventional radiology. The recent shortage is not the first one for contrast media in general [9] and possibly will not be the last. Although many review articles concerning the shortage of contrast media have been published [5,9], there are still several questions open. The goal of this narrative review is to give a comprehensive overview of the present shortage including the

Abbreviations: ACR, American College of Radiology; CECT, contrast enhanced computed tomography; CI-AKI, contrast-induced acute kidney injury; CM, contrast medium; CTA, computed tomography angiography; EHR, Electronic health record; HU, Hounsfield Units; ICM, iodinated contrast medium; MRI, magnetic resonance imaging; NECT, non-contrast-enhanced computed tomography.

* Corresponding author at: Department of Diagnostic, Interventional and Pediatric Radiology, University Hospital Bern, Freiburgstrasse 10, CH-3010 Bern, Switzerland.

E-mail address: Ingrid.boehm@insel.ch (I.B. Boehm).

https://doi.org/10.1016/j.ejrad.2023.110853
Received 8 April 2023; Received in revised form 20 April 2023; Accepted 26 April 2023
Available online 3 May 2023
0720-048X/

measurements to manage it, as well as to point out potential opportunities a reduced ICM usage could offer.

2. Material and methods

2.1. Search strategy and paper selection

We conducted a literature search using the online databases PubMed and Google Scholar. All papers published until February 2023 were included in the search. Google Scholar search was limited to title search. The following search terms were used, "contrast media" OR "contrast medium" AND "shortage".

In addition, we searched articles that deal with CM (contrast media) low-dose regimens and its advantages. Some papers come from other sources (e.g. references to PubMed publications). Moreover, we also searched for relevant information with the help of google (https://www.google.ch).

2.2. Eligibility criteria

Articles investigating the management of the current contrast media shortage were included. Excluded were articles that did not consider contrast media or where contrast media were not the focus. Articles that did not consider contrast media shortage or were focusing on shortage of other goods as well as articles that did not target contrast media reduction were excluded. News articles, editorials, letters and citations were also left out.

3. Results

3.1. Paper selection

We excluded 96 of 118 identified papers (Fig. 1). The remaining 22 papers [4–25] served as basis for the following analysis, and contain a variety of different study types such as retrospective studies (n = 4), clinical perspectives (n = 3), special reports (n = 2), review articles (n = 5; including two narrative reviews), and others (n = 8). All articles are either published in the USA (n = 17) or in Australia (n = 5). Nineteen articles have been published in 2022 and three in 2023. In 17 articles, we found the lockdown in a General Electric Health care (GE) production facility in Shanghai as reason for the current shortage, while five other articles do not mention a reason.

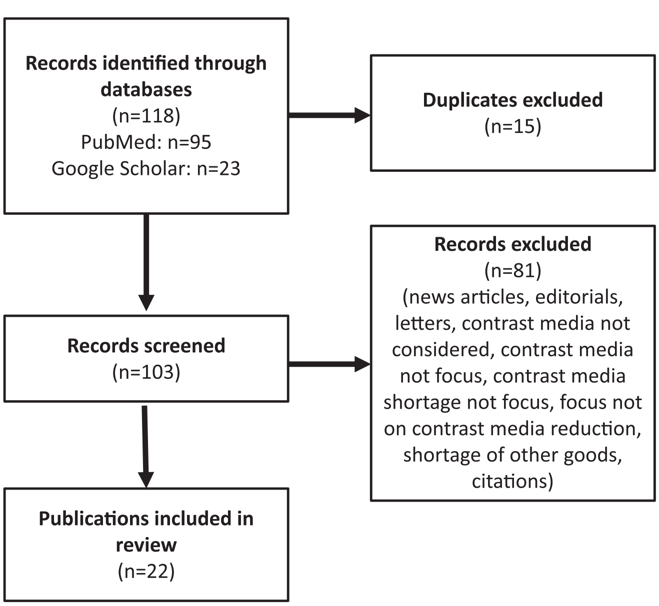

Fig. 1. Paper selection flow diagram.

3.2. Affected contrast media and countries

All 22 included articles outline ICMs as primarily affected substances. GE first informed their customers in April 2022 about a shortage of Omnipaque® (iohexol) affected by the lockdown in Shanghai [10]. Shortly afterwards, several other ICMs such as iodixanol (Visipaque®, GE), iopamidol (Isovue®, Bracco Diagnostics), iopromide (Ultravist®, Bayer HealthCare) and ioversol (Optiray®, Guerbet) were reported short in supply [4]. These and more products faced a sudden rise in demand that could not be met on short term causing a chain reaction as many institutions tried to increase their inventories with alternative contrast agents [4]. In the United States, GEs Omnipaque® and Visipaque® make up more than 50% of the ICM market share. While Bracco Diagnostics Isovue® is responsible for another 45%, less than 5% are covered by other suppliers [26]. Bracco Diagnostics, Bayer and Guerbet all reported that they were not able to scale up production to meet the raised demand for ICM [6].

In May 2022, a GE representative said that there could also be supply bottlenecks in Europe (e.g. Germany) [27]. This scenario did not occur.

3.3. History of the ICM-shortage

Many health facilities operate on a just in time basis and therefore only have a few weeks of supply in stock [11]. As of July 2022, GE published a press release announcing its Shanghai facility is operating at full capacity again but a reduced availability is expected for some time [28].

As most health institutions were not prepared for a shortage of ICM, measurements had to be taken to stay operational. All of it while maintaining high-quality patient care. In response the American Journal of Radiology published a statement on how health care providers may face the crisis [12]. The Royal Australian and New Zealand College of Radiologists as well as authors from Yale have published further guidance on how to preserve ICM [4]. Following the persisting shortage, more publications discussing this issue have been released [5–25].

3.4. Strategies to solve the problem

In May 2022, the American College of Radiology (ACR) issued a statement with guidance on how to address the shortage [12]. In eight articles this guidance was considered [5,7,9,16,18,20,21,25], while two articles considered ICM conservation techniques of Yale School of Medicine [4,5]. We can discriminate two main strategies: 1) Reduction of the number of contrast-enhanced image-guided examinations and/or 2) reduction of the (single) ICM dose (Fig. 2).

3.4.1. Reduction of contrast enhanced image-guided examinations

Different interventions can result in a reduction of CECT (Fig. 2). The committee consists of an interprofessional team and has to oversee ICM supply and usage within an institution to improve triage, for example by reducing the number of CECT by requiring approval of a radiologist or a radiology registrar before performing a scan or by only allowing referrals from experienced doctors [5,7].

Eibschutz et al. mentioned that launching an institution-wide committee is critical to establish a common approach of all departments involved [9]. The committee should overlook CM use and availability within an organization to create plans for CM reduction by interprofessional communication [6,9,20]. Many indications allow the use of alternative imaging techniques/modalities such as non-contrast-enhanced CT (NECT), MRI, ultrasound with or without contrast agents and nuclear medicine scanning methods. The availability and capacity of alternative imaging modalities is essential.

Improving triage to CECT can be achieved by changing guidelines and for example require senior doctors to approve CECT orders or have radiologists or radiology registrars approval [5]. Moreover, improved triage can also be achieved by simply using digital alerts to remind

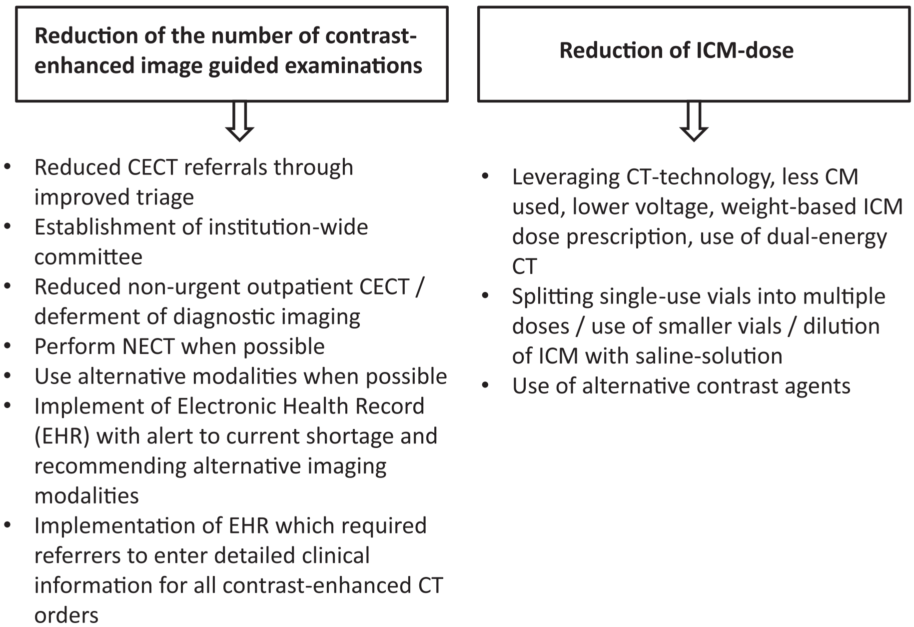

Fig. 2. Summary of possible interventions according to analysed articles [4–25]. The first authors of the papers are mentioned.

referrers of the tightness of ICM when ordering an examination [16]. Deferment of diagnostic imaging should whenever possible be avoided.

3.4.2. Reduction of ICM dose

The ICM volume per examination can be reduced by lowering tube voltage or weight-based dosing [7,9]. While in many institutions CT scanners have been modernized, from single-energy CT to dual-energy CT for example, protocols often have not been adapted [5]. With lower tube voltage ICM volume can be reduced by up to 66% [10]. The use of lower tube voltage results in increased image noise [29]. However newer CT scanners with higher tube current capacities and iterative image reconstruction software are able to reduce image noise [29]. In CT angiography (CTA) for example this allows a reduction of contrast media of up to 50% (140 instead of 280 mgI/kg body weight, for example) [30]. Amukotuwa et. al. reported a reduction from 75 ml to 50 ml of ICM for CT pulmonary angiogram and brain and neck CT angiography and from 60 ml to 40 ml in brain CT perfusion, all of it while not compromising diagnostic image quality [5]. The optimal injection protocol varies depending on the type of examination. De Cecco et al. were able to lower contrast media dose to 15 ml with 70 kV for the ascending aorta while still reaching diagnostic enhancement of 350 Hounsfield Units [31].

Optimizing the amount of waste is another approach. This means we can reduce waste either by using smaller vials per examination or by splitting single vials into multiple doses if the necessary precautions can be taken [4,6–8,10,11,15,18,20,22,23,25].

3.5. Effectiveness

Of 22 articles analyzed, 12 provide outcomes regarding the effectiveness. Depending on composition of the interventions and the period analysed, the reduction of CECTs performed was between 12% [16] and 85% [5]. A reduction of 12% was achieved by implementing an EHR alarm system [16]. Reduction of ICM volume used per examination was between 16% and 93% [5] depending on type of examination. Overall reduction of the ICM usage in the analysed articles ranges between 50% [23] and 80% [25] (see in Table 1).

Five articles state that the reduction of the number of CECTs performed contributes more to the overall result than volume reduction does [7,13,14,20,23].

Table 1
Summary of the effect of the specific interventions as presented in the literature. We distinguish between reduced dose per examination, reduced number of examinations and the total reduction from these two parameters.

First author (year) [ref]	Reduced CM dose	Reduced examination frequency	Total ICM reduction
Forouzandeh F et al. 2022 [15]			46%
Allen L et al. 2022 [8]			50%
Salazar G et al. 2022 [20]			50%
Barreto I et al. 2022 [10]	66%	34%	
Amukotuwa SA et al. 2022 [5]	93%	85%	
Amukotuwa SA et al. 2022 [7]	16%	59%	65%
Amukotuwa SA et al. 2022 [13]	16%	61%	67%
Bammer R et al. 2022 [21]	88%	75%	72%
Davenport MS et al. 2022 [14]	25%	78%	83%
Gopireddy DR et al. 2023 [25]			80%
Rosander A et al. 2023 [23]		43%	50%
Glazer D et al. 2023 [16]		12%	

3.6. Low-dose CM regimens before the shortage occurred

Reduced ICM doses were already proposed for various image-guided examinations before the current supply shortage. Reason for this measure is the improved safety of contrast agent use in various patients at risk such as contrast-induced acute kidney injury (CI-AKI), renal dysfunction, or allergies to contrast agents [32]. For example, the use of lower tube voltage in combination with iterative imaging reconstruction and lowering contrast dose with dual-energy CT as mentioned above has been proposed [29]. Other strategies to save ICMs are injection of diluted iodinated contrast, the use of alternative contrast agents or intravascular ultrasound guidance in percutaneous coronary interventions [32,33]. A more practical approach for cardiac catheterization for example is careful review of patients records in order to reduce the volume and frequency of "puffs of contrast", use of smaller catheters, use of contrast-saving devices as well as modern imaging devices [34].

3.7. Benefits of low-dose ICM usage

The reduction of use of ICM and the adjustment of CECT guidelines as well as number of CECT performed overall with the described interventions leads to less exposure of iodine and radiation [7]. As an example, reducing the peak kilovoltage can decrease the radiation dose by up to 66% [4].

The use of ICM comes with potential adverse effects [35–39]. The risk for contrast-induced acute kidney injury (CI-AKI) depends on background risk factors, such as pre-existing renal diseases, and type and dose of contrast medium used and ranges from 0% to 24% [35]. The amount of contrast medium used correlates with the risk of CI-AKI and is higher in the presence of other risk factors (congestive heart failure, nephrotoxic drugs, diabetes, anaemia, age, etc.) [36].

Allergic type reactions caused by non-ionic ICM are uncommon (0,6%) [40]. Non-allergy (allergic-like) reactions are a bit more common with 0,16%-7,7% [41]. The differentiation of allergic or non-allergic reactions often lacks proper diagnosis and is therefore discussed [37]. Some authors explain a reaction without primary sensitization with a cross-reactivity [42]. It has only been known for a few years that ICMs pollute the environment and get into the groundwater. What significance this has for humans and nature is largely unknown so far. It is possible that the ingestion of small amounts of ICM via drinking water may lead to silent sensitization in humans [43]. If patients with silent sensitization receive an ICM for the first time in their lives, they might unexpectedly react with an allergic reaction. Park et. al. have shown in their study that a reduction in dose and injection speed has led to a lower rate of acute hypersensitivity reactions [44].

Besides primary sensitization, increasing ICM pollution in source and tap water may have additional effects on human health, as evidence indicates that ICM transformation products are toxic [45]. In a study performed in Jiangsu province, China Cheng et. al. found ICM concentration in source water to range from 14.2 to 138 ng/L while studies from other countries reported even higher concentrations ranging from 4.9 to 305 ng/L [46]. Taking measures to reduce ICM usage in general leads to less of it in wastewater and therefore in ground and drinking water.

The iodine content of ICMs can lead to thyroid gland problems including thyroid toxic crisis. Patients suffering from hyperthyroidism are at increased risk [47]. Other groups at risk are patients with multinodular goitre or thyroid autonomy, in particular if they are elderly [47]. Patients with manifest hyperthyroidisms should not receive ICM at all, while patients undergoing radioactive iodine treatment should not receive ICM for two months before the treatment [47]. Dependent on recommendations of different medical societies including the World Health Organization (WHO), the daily iodine intake is set at about 150 µg per day in adults [48]. ICMs contain approximately 13,500 µg of free iodine and 15–60 g of bound iodine [47,49]. Rhee et. al. found a significant association between incident hyperthyroidism and ICM exposure [49]. The authors concluded that less iodine is safer.

Pregnant and breastfeeding women are a vulnerable group of patients. The use of ICM is subject to a very strict indication, i.e. only if the mother's life is vitally threatened the injection of an ICM is allowed [50]. In other words, contrast-enhanced image-guided examinations are rare in this group. If an examination with ICM is mandatory, the use of a low-dose protocol would be an advantage for the foetus or the new-born baby. Iodine is essential for foetal brain development and can be disrupted by ICM examinations in pregnant women [51]. The body reacts to elevated levels of iodine by inhibiting thyroid hormone synthesis and therefore prevent hyperthyroidism, a phenomenon called Wolff-Chaikoff [52]. This effect applies both to the foetal and the maternal thyroid gland [51]. Van Welie et. al. found that the use of ICM prior or during pregnancy leads to potential higher risk of thyroid dysfunction in offspring [51].

Reducing the number of CECTs and implementing more effective guidelines leads also to direct cost saving and reduces scan turn-around time and length of stay which results in reduced indirect costs [7].

4. Discussion

The supply shortages of contrast media of 2021/22 were or are a challenge for radiology. The largest producer of ICM worldwide is GE who operates its main production facility for iohexol (Omnipaque®) in Shanghai [7]. The closure of the facility in the context of Covid-19 pandemic lockdowns has caused a worldwide disruption of ICM supply. Despite the global interconnectedness of the economy, it was mainly the USA and Australia that were affected. Why the European market was/is not affected could not be clarified based on the literature. For Europe (Germany), there were fears that there could be a supply bottleneck for contrast media [27]. Since this scenario did not occur, the production capacities were sufficient to prevent this bottleneck.

Initially, iohexol was affected from the shortage. To compensate for the supply bottlenecks of this ICM, other available contrast media were ordered. This in turn resulted in supply shortages of iodixanol, iopamidol, iopromide and ioversol as well, because production capacities could not be increased at short notice [4].

In response to the current ICM crisis, the American College of Radiology (ACR) as well as many authors have published recommendations on how to address this emergency [4–25].

In this review, we found that the measurements mentioned can be discriminated into two groups: 1) reduction of the number of contrast-enhanced image-guided examinations and/or 2) reduction of ICM dose. Although both groups have resulted in significant reduction of overall ICM use, reducing the number of contrast-enhanced image-guided examinations, with alternative imaging for example, has proven to have a higher impact on overall ICM use [13]. The reduction achieved in the analysed articles ranges between 50% [23] and 80% [25].

Moreover, even before the shortage of 2022, there were efforts to reduce the number of CECTs [53] or to reduce the dosage of the contrast medium [54]. Although the article by Eibschutz et al. [9] is entitled "How low can we go?", the publication does not address this issue. In other words, we do not learn how low one can reduce the contrast agent dose in order to still get high-quality imaging. Other publications do also not address this question [4,6,11,12,17–19,22,24]. Therefore, preclinical and clinical studies are necessary to answer this question. Possibly, artificial intelligence (AI) could also offer a solution [55].

Adjusted ICM usage and thus a reduction of dependence in future shortages also has positive effects on patient safety. Therefore, the application of a reduced dose of contrast agent or the reduced performance of CECTs harbors the chances of a lower frequency / severity of adverse drug reactions (Table 2). With lower tube voltage, patients are

Table 2
Summary of chances of low-dose contrast applications.

Category	Effect(s)
Radiation dose	Reduced when a lower tube voltage is used
CI-AKI	The lower the ICM-dose used, the lower the frequency
Hypersensitivity reactions	Frequency decreases
ICM-induced thyroid disturbance (including thyrotoxicosis)	In patients at risk less frequent
Pregnant and breastfeeding women	Decreased risk for the foetus or the baby
Contamination of drinking- / groundwater	Less pronounced

exposed to a lesser radiation dose. In addition, the risk of contrast-induced acute kidney injury (CI-AKI) is reduced by lower doses. Patients with pre-existing risk factors such as renal insufficiency, congestive heart failure, drugs, anaemia, diabetes or old age benefit in particular from reducing doses and alternative imaging modalities. Another complication that can be reduced is the allergic-type reaction and the allergic-like hypersensitivity reactions, the occurrence of which can also be reduced by lower doses. More than 35 years ago, in a small patient group low-dose CT (i.e. myelography) has been performed [56]. Even under this pilot-project-condition, the authors recognized remarkably few adverse effects.

A possible sensitization with ICM containing drinking water would also be less likely as the portion of ICM in drinking water decreases with lower amounts used. Patients with pre-existing thyroid dysfunction are at increased risk for contrast medium-induced thyrotoxicosis or should not receive ICM at all. Overall, patients can benefit from fewer ICM examinations and fewer ICM used per examination. However, all these reductions must be made under strict monitoring of patient safety, outcome, and long-term effects.

The number of publications on this topic limits this review. Most articles deal with short-term effects of the current ICM shortage and have therefore been discussing short-term measurements to deal with the problem. Only 12 out of the 22 articles present specific and quantifiable results as shown in Table 1 [5,7,8,10,13–16,20,21,23,25]. Although nine articles mention the potential long-term benefits the insights and knowledge gained through the current crisis offers, more studies are needed to assess the long-term patient outcomes [4,7,9,10,15,18,19,21,23]. Therefore, it is necessary to conduct further studies of higher quality to research the effectiveness and patient safety of the proposed measures as well as to research possible alternative measures to reduce contrast media use in the future.

Although there are many reviews dealing with shortage of contrast media [5,9,23–25], several questions remain unanswered. The articles published, primarily deal with short-term management of the crisis or derive measures for future ICM shortage management, primarily from procurement policy [9]. Compared to the other articles (including reviews) [4–25] our paper deals with further advantages of a general reduction of ICM in addition to reducing the dependency on certain companies/production sites during a future potential ICM shortage. The measures described to reduce the use of contrast media in "emergency operations" have shown that hospital operations would get by with less contrast media and that patients and the environment could benefit from this in addition to procurement policy.

5. Conclusion

The 2022 ICM shortage caused by Covid-19 related lockdowns in Shanghai China has forced health care providers to come up with ICM conservation strategies. The measurements implemented have led to a noticeable reduction of overall ICM use. Although supply is expected to go back to normal, it is a good opportunity to reconsider protocols and use of contrast-enhanced imaging in general to reduce ICM use as it lessens dependence on suppliers and benefits patients. To achieve this, further studies regarding patient outcomes and long-term effects are needed. Including all aspects, the shortage is a challenge in clinical radiology, but on the other side the reduced ICM use has several chances or advantages such as reduced costs, reduced environmental impact from ICMs, lower incidences of adverse events with respect to hypersensitivity reactions, CI-AKI, thyroid gland problems, and increased safety for children, pregnant and breastfeeding women.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

David R. Koeppel: Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft. **Ingrid B. Boehm:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R.W. Katzberg, "Acute Reactions to urographic contrast medium: incidence, clinical characteristics, and relationship to history of hypersensitivity states"—A commentary, AJR. Am. J. Roentgenol. 190 (2008) 1431–1432, https://doi.org/10.2214/AJR.07.3606.

[2] L. Schöckel, G. Jost, P. Seidensticker, P. Lengsfeld, P. Palkowitsch, H. Pietsch, Developments in X-Ray Contrast Media and the Potential Impact on Computed Tomography, Invest. Radiol. 55 (2020) 592–597, https://doi.org/10.1097/RLI.0000000000000696.

[3] H.M. Dekker, G.J. Stroomberg, M. Prokop, Tackling the increasing contamination of the water supply by iodinated contrast media, Insights. Imaging. 13 (2022) 30, https://doi.org/10.1186/s13244-022-01175-x.

[4] J.J. Cavallo, J.K. Pahade, Practice Management Strategies for Imaging Facilities Facing an Acute Iodinated Contrast Media Shortage, AJR. Am. J. Roentgenol. 219 (2022) 666–670, https://doi.org/10.2214/AJR.22.27969.

[5] S.A. Amukotuwa, R. Bammer, D.M. Jackson, T. Sutherland, Iodinated contrast media shortage: Insights and guidance from two major public hospitals, J. Med. Imaging. Radiat. Oncol. 66 (2022) 946–956, https://doi.org/10.1111/1754-9485.13444.

[6] T.M. Grist, C.L. Canon, E.K. Fishman, M.P. Kohi, M. Mossa-Basha, Short-, Mid-, and Long-term Strategies to Manage the Shortage of Iohexol, Radiology. 304 (2022) 289–293, https://doi.org/10.1148/radiol.221183.

[7] S.A. Amukotuwa, D. Jackson, R. Bammer, Impact of iodinated contrast media conserving interventions and lessons for the future, J. Med. Imaging. Radiat. Oncol. (2022) 1754–9485, https://doi.org/10.1111/1754-9485.13458.

[8] L.M. Allen, J. Shechtel, K. Frederick-Dyer, L.T. Davis, L.S. Stokes, B. Savoie, S. Pruthi, C. Henry, S. Allen, S.R. Frazier, R.A. Omary, Rapid Response to the Acute Iodinated Contrast Shortage During the COVID-19 Pandemic: Single-Institution Experience, J. Am. Coll. Radiol. 19 (2022) 836–840, https://doi.org/10.1016/j.jacr.2022.05.005.

[9] L.S. Eibschutz, A. Gholamrezanezhad, How low can we go? Strategies and recommendations to combat the iodinated contrast shortage, Emerg. Radiol. 29 (2022) 925–928, https://doi.org/10.1007/s10140-022-02077-7.

[10] I.L. Barreto, J.R. Grajo, D.E. Brock, L. Magnelli, P. Patel, B. Hochhegger, A Health System's Response to the Ongoing Global Shortage of Iodinated Contrast Media, AJR. Am. J. Roentgenol. 219 (2022) 974–979, https://doi.org/10.2214/AJR.22.28060.

[11] L. Ananthakrishnan, F.U. Kay, E.A. Zeikus, E.S. Chu, J. Chang, J.D. Barr, N. M. Rofsky, S. Abbara, What the Baby Formula and Medical Contrast Material Shortages Have in Common: Insights and Recommendations for Managing the Iodinated Contrast Media Shortage, Radiol. Cardiothorac. Imaging. 4 (2022) e220101.

[12] C.L. Wang, D. Asch, J. Cavallo, J.R. Dillman, J.H. Ellis, M.M. Forbes-Amrhein, L. A. Gilligan, P. Krishnan, R.J. McDonald, J.S. McDonald, B.L. Murphy, B.M. Mervak, J.H. Newhouse, J.K. Pahade, A. Sumkin, J.C. Weinreb, S. Weinstein, M. S. Davenport, Statement from the ACR Committee on Drugs and Contrast Media on the Intravenous Iodinated Contrast Media Shortage, J. Am. Coll. Radiol. 19 (2022) 834–835, https://doi.org/10.1016/j.jacr.2022.05.006.

[13] S.A. Amukotuwa, D. Jackson, R. Bammer, Iodinated Contrast Media Conservation Measures During a Global Shortage: Effect on Contrast Media Use at a Large Health System, AJR. Am. J. Roentgenol. 219 (2022) 983, https://doi.org/10.2214/AJR.22.28080.

[14] M.S. Davenport, P. Chu, T.P. Szczykutowicz, R. Smith-Bindman, Comparison of Strategies to Conserve Iodinated Intravascular Contrast Media for Computed Tomography During a Shortage, JAMA. 328 (2022) 476, https://doi.org/10.1001/jama.2022.9879.

[15] F. Forouzandeh, S.G. Al-Kindi, M. Rana, C. Lowry, D.I. Simon, M.H. Shishehbor, Navigating Through Contrast Media Shortage: Feasible Without Delaying Patient Care, JACC. Cardiovasc. Interv. 15 (2022) 1393–1394, https://doi.org/10.1016/j.jcin.2022.05.040.

[16] D.I. Glazer, D.J. Lucier, R.C. Sisodia, A. Sharma, D.A. Gervais, L. Park, N. Abbasi, H.T. Hubbell, N. Kapoor, E.J. Flores, S. Saini, R. Khorasani, Electronic Health Record Order Entry-Based Interventions in Response to a Global Iodinated Contrast Media Shortage: Impact on Contrast-Enhanced CT Utilization, AJR. Am. J. Roentgenol. 220 (2023) 134–140, https://doi.org/10.2214/AJR.22.28143.

[17] L. Kohan, Z. Pellis, D.A. Provenzano, A.C.S. Pearson, S. Narouze, H.T. Benzon, American Society of Regional Anesthesia and Pain Medicine contrast shortage position statement, Reg. Anesth. Pain. Med. 47 (2022) 511–518, https://doi.org/10.1136/rapm-2022-103830.

[18] N.A. Keefe, K.R. Desai, M.P. Kohi, G.M. Salazar, Mitigation Strategies for Interventional Radiology During a Global Contrast Media Shortage, J. Vasc. Interv. Radiol. 33 (2022) 1021–1024, https://doi.org/10.1016/j.jvir.2022.05.011.

[19] L.H. Tu, J.E. Miller, H.P. Forman, The Critical Shortage of Iodinated Contrast Material — Will Value Prevail? N. Engl. J. Med. 387 (2022) 491–493, https://doi.org/10.1056/NEJMp2206996.

[20] G. Salazar, M. Mossa-Basha, M.P. Kohi, L.M. Burke, Short-Term Mitigation Steps During the Iohexol Contrast Shortage: A Single Institution's Approach, J. Am. Coll. Radiol. 19 (2022) 841–845, https://doi.org/10.1016/j.jacr.2022.05.004.

[21] R. Bammer, S.A. Amukotuwa, Navigating Supply Chain Disruptions of Iodinated Contrast Agent for Neuroimaging and How Business Intelligence Can Help the Decision Process, AJNR. Am. J. Neuroradiol. 43 (2022) 944–950, https://doi.org/10.3174/ajnr.A7544.

[22] N.M. Schuster, F.M. Ahadian, Z. Zhao, W.M. Hooten, D.C. Miller, J.M. Hagedorn, A. Gulati, B.S. Duszynski, Z.L. McCormick, A.S. Nagpal, Best practices for interventional pain procedures in the setting of an iodinated contrast media shortage: A multisociety practice advisory, Interventional. Pain. Medicine. 1 (2022), 100122, https://doi.org/10.1016/j.inpm.2022.100122.

[23] A. Rosander, R. Andrade, J. Concepcion, L. Woodley, W. Havron, A. Elkbuli Institutional response to the, iodinated contrast shortage: A narrative review, Am. J. Emerg. Med. 64 (2023) (2022) 62–66, https://doi.org/10.1016/j.ajem.2022.11.016.

[24] C. Yu, Lessons from the contrast dye shortage during COVID-19: A narrative review, Medicine. (Baltimore). 101 (2022) e32286.

[25] D.R. Gopireddy, M. Virarkar, S.S.R. Vulasala, D. Caro, A. Norse, D. Rao, Metrics-driven successful strategy by emergency and radiology driven task force to mitigate global CT contrast media shortage in a safety net hospital, J. Clin. Imaging. Sci. 13 (2023) 2, https://doi.org/10.25259/JCIS_116_2022.

[26] Drug Shortage: Iohexol (Omnipaque) and Iodixanol (Visipaque), (2022). https://s3.amazonaws.com/rdcms-snmmi/files/production/public/Vznt_MS_%20Iohexol%20%28Omnipaque%29%20and%20iodixanol%20%28Visipaque%29%20solution_0522%20_update.pdf (accessed February 7, 2023).

[27] Deutsche Krankenhausgesellschaft warnt vor Kontrastmittel-Engpässen im Juni, Universimed. (2022). https://www.universimed.com/de/deutsche-krankenhausgesellschaft-kontrastmittel-engp%C3%A4ssen-juni-144115 (accessed March 29, 2023).

[28] GE Healthcare update on iodinated contrast media, (2022). https://www.ge.com/news/press-releases/ge-healthcare-update-on-iodinated-contrast-media (accessed December 13, 2022).

[29] D. Fornell, Strategies to Lower CT Contrast Dose and Track Usage, (2019). https://www.itnonline.com/article/strategies-lower-ct-contrast-dose-and-track-usage (accessed February 7, 2023).

[30] S. Oda, D. Utsunomiya, H. Yuki, N. Kai, M. Hatemura, Y. Funama, M. Kidoh, M. Yoshida, T. Namimoto, Y. Yamashita, Low contrast and radiation dose coronary CT angiography using a 320-row system and a refined contrast injection and timing method, J. Cardiovasc. Comput. Tomogr. 9 (2015) 19–27, https://doi.org/10.1016/j.jcct.2014.12.002.

[31] C.N. De Cecco, U.J. Schoepf, New contrast injection strategies for low kV and keV imaging, accessed February 27, 2023, Applied. Radiology (2018), https://appliedradiology.com/articles/new-contrast-injection-strategies-for-low-kv-and-kev-imaging.

[32] G.J. Nadolski, S.W. Stavropoulos, Contrast alternatives for iodinated contrast allergy and renal dysfunction: Options and limitations, J. Vasc. Surg. 57 (2013) 593–598, https://doi.org/10.1016/j.jvs.2012.10.009.

[33] J. Mariani, C. Guedes, P. Soares, S. Zalc, C.M. Campos, A.C. Lopes, A.G. Spadaro, M.A. Perin, A.E. Filho, C.K. Takimura, E. Ribeiro, R. Kalil-Filho, E.R. Edelman, P. W. Serruys, P.A. Lemos, Intravascular Ultrasound Guidance to Minimize the use of Iodine Contrast in Percutaneous Coronary Intervention: The MOZART Randomized Controlled Trial, JACC. Cardiovasc. Interv. 7 (2014) 1287–1293, https://doi.org/10.1016/j.jcin.2014.05.024.

[34] F. Latif, H.T.D. Truong, Practical Techniques to Reduce Contrast Volumes in the Cardiac Catheterization Laboratory, Society for Cardiovascular Angiography & Interventions. (2020). https://scai.org/practical-techniques-reduce-contrast-volumes-cardiac-catheterization-laboratory (accessed February 7, 2023).

[35] M. Hossain, E. Costanzo, J. Cosentino, C. Patel, H. Qaisar, V. Singh, T. Khan, J. Cheng, A. Asif, T. Vachharajani, Contrast-Induced nephropathy: Pathophysiology, risk factors, and prevention, Saudi. J. Kidney. Dis. Transpl. 29 (2018) 1, https://doi.org/10.4103/1319-2442.225199.

[36] R. Mehran, E. Nikolsky, Contrast-induced nephropathy: Definition, epidemiology, and patients at risk, Kidney. Int. Suppl. 69 (2006) S11–S15, https://doi.org/10.1038/sj.ki.5000368.

[37] I. Böhm, J. Morelli, K. Nairz, P. Silva Hasembank Keller, J.T. Heverhagen, Myths and misconceptions concerning contrast media-induced anaphylaxis: a narrative review, Postgrad Med. 129 (2017) 259-266. Doi: 10.1080/00325481.2017.1282296.

[38] M.J. Torres, A. Trautmann, I. Böhm, K. Scherer, A. Barbaud, S. Bavbek, P. Bonadonna, J.R. Cernadas, A.M. Chiriac, F. Gaeta, A.M. Gimenez-Arnau, H. Kang, E. Moreno, K. Brockow, Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity, Allergy. 76 (2021) 1325–1339, https://doi.org/10.1111/all.14656.

[39] I. Böhm, J.T. Heverhagen, K.J. Klose, Classification of acute and delayed contrast media-induced reactions: proposal of a three-step system: CM-hypersensitivity classification, Contrast. Media. Mol. Imaging. 7 (2012) 537–541, https://doi.org/10.1002/cmmi.1475.

[40] C.L. Wang, R.H. Cohan, J.H. Ellis, E.M. Caoili, G. Wang, I.R. Francis, Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions, AJR. Am. J. Roentgenol. 191 (2008) 409–415, https://doi.org/10.2214/AJR.07.3421.

[41] S.-Y. Lee, K.-W. Lim, Y.-S. Chang, Radiocontrast media hypersensitivity in the Asia Pacific region, Asia. Pac. Allergy. 4 (2014) 119, https://doi.org/10.5415/apallergy.2014.4.2.119.

[42] A.A. Schmid, J.N. Morelli, M.N. Hungerbühler, I.B. Boehm, Cross-reactivity among iodinated contrast agents: should we be concerned? Quant. Imaging. Med. Surg. 11 (2021) 4028–4041, https://doi.org/10.21037/qims-20-1325.

[43] I. Böhm, Iodinated X-ray contrast media in aquatic environment in general and in drinking water in particular: A possible source for the primary sensitization of patients, Chemosphere. 194 (2018) 28–29, https://doi.org/10.1016/j.chemosphere.2017.11.154.

[44] H.J. Park, J.H. Son, T.-B. Kim, M.K. Kang, K. Han, E.H. Kim, A.Y. Kim, S.H. Park, Relationship between Lower Dose and Injection Speed of Iodinated Contrast Material for CT and Acute Hypersensitivity Reactions: An Observational Study, Radiology. 293 (2019) 565–572, https://doi.org/10.1148/radiol.2019190829.

[45] A. Sengar, A. Vijayanandan, Comprehensive review on iodinated X-ray contrast media: Complete fate, occurrence, and formation of disinfection byproducts, Sci. Total. Environ. 769 (2021), 144846, https://doi.org/10.1016/j.scitotenv.2020.144846.

[46] X. Cheng, Y. Xia, Q. Ji, Q. Ji, H. Li, J. Guo, S. Li, S. Yang, L. Zhang, H. He, Occurrence and risk of iodinated X-ray contrast media in source and tap water from Jiangsu province, China,. J. Hazard. Mater. 444 (2023), 130399, https://doi.org/10.1016/j.jhazmat.2022.130399.

[47] H.S. Thomsen, S.K. Morcos, A.J. van der Molen, Effect of iodinated contrast media on thyroid function in adults, Eur. Radiol. 14 (2004) 902–907, https://doi.org/10.1007/s00330-004-2238-z.

[48] H. Bürgi, Iodine excess, Best. Pract. Res. Clin. Endocrinol. Metab. 24 (2010) 107–115, https://doi.org/10.1016/j.beem.2009.08.010.

[49] C.M. Rhee, Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism, Arch. Intern. Med. 172 (2012) 153, https://doi.org/10.1001/archinternmed.2011.677.

[50] ESUR Guidelines on Contrast Agents, (2018). https://www.esur.org/wp-content/uploads/2022/03/ESUR-Guidelines-10_0-Final-Version.pdf (accessed February 23, 2023).

[51] N. van Welie, M. Portela, K. Dreyer, L.J. Schoonmade, M. van Wely, B.W.J. Mol, A. S.P. van Trotsenburg, C.B. Lambalk, V. Mijatovic, M.J.J. Finken, Iodine contrast prior to or during pregnancy and neonatal thyroid function: a systematic review, Eur. J. Endocrinol. 184 (2021) 189–198, https://doi.org/10.1530/EJE-20-0627.

[52] P.H.K. Eng, G.R. Cardona, S.-L. Fang, M. Previti, S. Alex, N. Carrasco, W.W. Chin, L. E. Braverman, Escape from the Acute Wolff-Chaikoff Effect Is Associated with a Decrease in Thyroid Sodium/Iodide Symporter Messenger Ribonucleic Acid and Protein, Endocrinology. 140 (1999) 3404–3410.

[53] D.J. Brenner, Minimising medically unwarranted computed tomography scans, Ann. ICRP. 41 (2012) 161–169, https://doi.org/10.1016/j.icrp.2012.06.004.

[54] J. Haubold, R. Hosch, L. Umutlu, A. Wetter, P. Haubold, A. Radbruch, M. Forsting, F. Nensa, S. Koitka, Contrast agent dose reduction in computed tomography with deep learning using a conditional generative adversarial network, Eur. Radiol. 31 (2021) 6087–6095, https://doi.org/10.1007/s00330-021-07714-2.

[55] G. Azarfar, S.-B. Ko, S.J. Adams, P.S. Babyn, Applications of deep learning to reduce the need for iodinated contrast media for CT imaging: a systematic review, Int. J. CARS. (2023), https://doi.org/10.1007/s11548-023-02862-w.

[56] H. Wang, A.E. Rosenbaum, M.L. Updike, A.J. Kumar, S.J. Zinreich, H.S. Ahn, W. S. Kim, Low dose cervical CT myelography. How acceptable are adverse effects at this juncture? Acta. Radiol. Suppl. 369 (1986) 539–541.