ORIGINAL ARTICLE

Oman Medical Journal [2017], Vol. 32, No. 5: 371-377

Awareness and Knowledge of Ionizing Radiation Risks Between Prescribed and Self-Presenting Patients for Common Diagnostic Radiological Procedures in Bahrain

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ARTICLE INFO

Article history:
Received: 25 January 2017
Accepted: 19 July 2017

Online:
DOI 10.5001/omj.2017.72

Keywords:
Ionizing Radiation; Radiological Technology; Self-presented Patients.

ABSTRACT

Objectives: Between 20 to 50% of medical imaging examinations are considered inappropriate, and unnecessary ionizing radiation exposures may lead to cancer. We hypothesized that Bahraini patients who self-present for ionizing radiation procedures are not aware of, and lack the requisite knowledge of, the inherent risks associated with their use than patients prescribed for diagnostic purposes. We attempted to examine and compare the awareness and knowledge of the associated risks of ionizing radiation in common diagnostic radiological procedures between prescribed and self-presenting patients in Bahrain. ***Methods***: A cross-sectional survey was carried out among 416 Bahraini patients attending the radiology department of the Salmaniya Medical Complex (SMC), a secondary health care center, who had been referred by primary care physicians or self-presented to the center. Data was collected via face-to-face interviews. ***Results:*** Prescribed patients (n = 358) had a better awareness than self-presenting (n = 58) patients on all ionizing radiation awareness statements (i.e., risks, permissible levels, willingness to undergo the procedure, and preference for a clinical examination over a radiological procedure) ($p < 0.050$). Of the 10 knowledge statements, the prescribed patients agreed on four statements than the self-presenting patients: preventing or minimizing exposure improves health, people can prevent or minimize exposure, a lifelong health concern, and radiological procedures offer best diagnoses compared to medical tests or procedures ($p < 0.050$). ***Conclusions:*** Bahraini patients who reported to SMC lack awareness and knowledge on ionizing radiation. The proportion of appropriate responses to awareness and knowledge questions were paltry for self-presenting patients and deficient for the prescribed patients in the knowledge segment alone.

Diagnostic radiology plays an essential role in medical practice and uses ionizing and non-ionizing radiation. Ultrasound and magnetic resonance imaging (MRI) are non-ionizing and are not associated with any known adverse effects or health risks as they utilize sound waves and magnetic fields, respectively. Whereas the use of gamma rays and X-rays in diagnostic radiological procedures (i.e., angiography, mammography, fluoroscopy, computed tomography (CT), nuclear medicine, and radiographic imaging) are risky and can have harmful results due to their ionizing effect.[1] The risk of inducing biological effects increases as the dose increases (dose response), increasing the lifetime risk of cancer. The lag period between radiation exposure and cancer diagnosis is typically five years but can extend to one or two decades, or more, in most cases.[2] Worldwide, radiation exposure from medical imaging may be responsible for 1–3% of cancers.[3] Children are particularly prone to ionizing radiation as the molecular processes within the brains of children are not yet complete.[4]

Radiation protection (RP) endorses no explicit "safe" radiation level. Nonetheless, RP standards for public and radiation workers are recommended

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by the International Commission on Radiological Protection (ICRP).[5] RP emphasizes the safe and controlled use of ionizing radiation, and its use for any radiological procedure for medical diagnosis should be kept as low as reasonably achievable.[6] RP in medicine hinges on the concepts of justification and optimization. While many efforts have been put forth for optimization, less has been committed to justification.[7,8] Justification refers to the appropriateness and dose of ionizing radiation in a radiological procedure based on the patient's brief clinical history.[9] The potential health benefits should almost always outweigh the potential risks of radiation exposure. The unit of measurement for radiation dose, commonly referred to as effective dose, is millisievert (mSv). The ICRP laid maximum limits for radiation exposure for practical purposes. For a general person, the maximum exposure over one year is 1 mSv. For instance, a chest X-ray is 0.1 mSv, a CT scan of the head is 2.0 mSv, and barium swallow fluoroscopy is 1.5 mSv.[5]

A physician's request for radiological examination should have sufficient clinical information on the patient, the requested procedure, position required, and the clinical query. Additionally, it must comply with the clinical guidelines.[10] Sources suggest that a significant fraction (20–50%) of medical imaging examinations may be inappropriate.[11,12]

Patients seek their physician's care and advice for ailments where clinical and physical examinations are required. In general, the need for a medical imaging procedure may not arise in all patients, and they are diagnosed without exposure to unnecessary ionizing radiation. Although it is the physician's decision to seek a radiological opinion for the patient, self-presentation[13] occurs when patients' refer themselves for a procedure and appeal for a radiology service as a psychological reassurance for themselves and is associated with a prevailing culture in certain communities. From the patients' perspective, non-referral for a medical imaging procedure means that the physician has neglected them.[14] Although medical imaging procedures do not provide any relief and are not considered a treatment, some patients have faith in medical imaging procedures as a vital tool.[15] This mindset is of concern. It implies that patients who self-present for medical imaging procedures are not aware of the referral system, radiation risks, and the economic burden associated with their use and overuse.[10]

The Kingdom of Bahrain is an archipelago made up of 33 islands located in the Arabian Gulf with a total area of 780 km^2. The population is around 1.3 million, which includes Bahrainis and multiethnic expatriates.[16] The Ministry of Health provides the primary health care services through 24 health centers and three health clinics. The Salmaniya Medical Complex (SMC) is the oldest and largest multispecialty health care facility providing emergency and secondary care to all Bahrainis and residents of Bahrain.[17]

There are no reports on the awareness and knowledge of the risks associated with ionizing radiation for radiological procedures in Bahrain, as well as comparisons between prescribed and self-presenting patients. We hypothesized that Bahraini patients who self-present are not aware of, and lack the requisite knowledge of, the inherent risks associated with the use of ionizing radiation compared to patients prescribed radiological procedures for diagnostic purposes. Therefore, we sought to examine and compare the awareness and knowledge of the associated risks of ionizing radiation between prescribed and self-presenting Bahraini patients at a secondary care center, SMC in Bahrain.

METHODS

This study was carried out after review and approval by the Institutional Research and Ethics Committee of the Ministry of Health, Bahrain, and the Research and Ethics Committee of the College of Health Sciences, University of Bahrain. A cross-sectional survey by a face-to-face interview rendered the data collection process. All consecutive Bahraini patients attending the radiology department of SMC either referred by primary health care physicians or directly reporting at the SMC due to an illness or self-presenting were included in the study. Parents responded if the patient was a minor (< 18 years of age). Pregnant women, patients attending the accident and emergency department, and non-Bahrainis were excluded from participating in the study.

A structured questionnaire was built following an in-depth literature review on ionizing radiation. The questionnaire was written in English language and translated into Arabic. To ensure originality of the questions, the questionnaire was back translated

from Arabic into English. For affirming face and content validity, the questionnaire was scrutinized by a panel of experts from the College of Health Sciences. Pretesting and piloting the questionnaire in 30 patients allowed for suitable modifications before embarking on the main study. The questionnaire was specific, realistic, measurable, and reliable that had an acceptable internal consistency (Cronbach's alpha = 0.72).

The survey questionnaire had four sections. The first part of the questionnaire gathered participants' demographics, including age, gender, and education level. The second part of the questionnaire, made up of three-items, collected participants' clinical information (i.e., purpose of hospital visit, any prior radiological procedure, and type of radiological procedure). The third and fourth parts of the questionnaire (multiple-choice questions) containing four and 10 items, respectively, were used to evaluate participants' radiation awareness and knowledge (e.g., health risks, prevention, maximum number of examinations per year). A standalone question on patient's preference to obtain information about ionizing radiation concluded the questionnaire.

The sample size was estimated using the following conservative parameters for prevalence: expected population proportion of 50%, 95% confidence interval, and a 5% precision estimate on two sides of the true population proportion. These parameters indicated a required sample size of 385.[18] The required sample was increased to 400 participants (a level of precision of 4.9% either side) to account for potential invalid or incomplete responses. An estimated sample size of 400 was considered adequate.

Informed consent was obtained from the patients without persuasion after describing the purpose of the study. Patient data was protected throughout the study and after. The data from the questionnaire was cleaned, coded, and entered into Microsoft Excel and exported to IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA) for statistical analysis. Descriptive statistics of frequency and percentages were used for the demographic characteristics. Differences in distribution of the awareness and knowledge responses between prescribed and self-presented patients were evaluated using the chi-squared test. Two-tailed tests were used, and a p-value < 0.050 was considered to be statistically significant.

Table 1: Demographics and clinical information of Bahraini patients for common radiological procedures (n = 416).

Characteristics	n (%)
Age, years	
< 10	19 (4.5)
10–19	47 (11.2)
20–29	99 (23.7)
30–39	81(19.4)
40–49	67 (16.1)
50–59	56 (13.4)
> 60	47 (11.2)
Gender	
Male	186 (44.7)
Female	230 (55.2)
Educational level	
No formal education	37 (8.8)
Primary school	106 (25.4)
High school	127 (30.5)
University graduate	146 (35.0)
Purpose of visiting the hospital	
Injury	155 (37.2)
Illness	204 (49.0)
General health check	57 (13.7)
Prior radiological procedure	
Yes	353 (84.8)
No	61 (14.6)
Did not remember	2 (0.4)
Type of radiological procedure	
Plain radiological procedure	276 (66.3)
Fluoroscopy	53 (12.7)
Computed tomography	44 (10.5)
Multiple procedures	43 (10.3)

RESULTS

A total of 416 patients completed the survey with complete responses. The majority of patients (n = 358) were in the prescribed group; 55.2% were female, and 44.7% were male [Table 1]. Half of the patients reported to SMC due to illness and 37.2% due to injury. Almost 85% had a radiological procedure before, and 14.6% reported for the first time. Two-thirds reported for the plain radiological procedure, 12.7% for a fluoroscopy, 10.5% for CT and, 10.3% for more than one procedure.

The level of awareness about the effect of ionizing radiation was evaluated using four statements [Table 2]. The prescribed patients had better awareness than the self-presented patients on all awareness statements concerning the risks,

Table 2: Patients awareness on ionizing radiation for common radiological procedures (n = 416).

Awareness question (appropriate response)	Prescribed patients with an appropriate response, %	Self-presented patients with appropriate response, %	95% CI	*p*-value
Are you aware of the risks of ionizing radiation? (Yes)	32.2	4.1	4.741– 37.6291	0.016
Are you aware of the maximum ionizing radiation dose permissible? (Yes)	85.0	1.8	72.878–87.408	< 0.001
Are you willing to undergo ionizing radiation procedure even if harmful? (No)	38.0	6.7	13.415– 41.318	< 0.001
Are you willing to undergo a clinical examination compared to a radiological procedure? (Yes)	66.7	3.4	37.281– 70.279	< 0.001

CI: confidence interval.

permissible levels of ionizing radiation, willingness to undergo ionizing radiation, and willingness to undergo a clinical examination rather than a radiological procedure ($p < 0.050$). The median appropriate responses to awareness for prescribed patients was 52.35 (interquartile range (IQR): 46.78) compared to 3.75 (IQR: 3.85) in the self-presented patients.

The level of knowledge about the effect of ionizing radiation was evaluated using 10 statements [Table 3]. A significantly greater percentage of prescribed patients agreed with the following four statements than the self-presented patients: Would preventing or minimizing ionizing radiation exposure improve a person's health? Can people prevent or minimize ionizing radiation? Is ionizing radiation a lifelong health concern, and does radiological procedure offer best diagnoses than other medical tests or medical procedures? ($p < 0.050$). Appropriate responses to other knowledge statements were not significant between the prescribed and self-presented patients. The median appropriate responses for prescribed patients was 17.45 (IQR: 40.9) and 3.75 (IQR: 5.83) for the self-presented patients.

Prescribed patients preferred to learn more about ionizing radiation from a health care provider (49.0%), internet-based resource (52.0%), or via a family member, friend, and other sources (21.0%). A lesser proportion of self-presenting patients preferred to learn more about ionizing radiation

Table 3: Knowledge on ionizing radiation between prescribed and self-presented Bahraini patients for common radiological procedures who attended a tertiary care center (n = 416).

Knowledge questions (appropriate response)	Prescribed patients with appropriate response, %	Self-presented patients with appropriate response, %	95% CI	*p*-value
Have you heard the term ionizing radiation before? (Yes)	12.5	4.1	-14.869–21.188	0.328
What does the term ionizing radiation mean? (Any type of energy that is capable of ionizing matter)	12.5	0.0	NA	NA
Is ionizing radiation dangerous to your health? (Yes)	6.3	0.7	-65.265–22.523	0.697
Would preventing or minimizing ionizing radiation exposure improve a person's health? (Yes)	45.4	7.5	20.916–47.640	< 0.001
What is the maximum number of radiological examinations permissible per year for the categories of radiological procedures? (Multiple responses)	5.8	1.7	-37.847–21.884	0.662
Can people prevent or minimize ionizing radiation? (Yes)	53.8	7.2	29.588–55.705	< 0.001
Is ionizing radiation a lifelong health concern? (Yes)	22.7	7.0	-1.206–24.689	0.052
Does radiological procedure offer best diagnoses than other medical tests or medical procedures? (Yes)	62.7	10.1	37.970–61.849	< 0.001
Can radiological procedures be avoided as part of diagnosis? (No)	22.4	3.4	-7.422–29.395	0.098
Can ionizing radiation reduce pain? (No)	6.7	1.7	-37.017–21.281	0.615

CI: confidence interval; NA :not available.

from a health care provider (19.0%), internet-based resource (12.0%), or via a family member, friend, and other sources (7.0%).

Overall, the appropriate responses to awareness and knowledge statements were higher for prescribed than self-presenting patients. However, no significant differences were found in the awareness and knowledge statements for the demographic characteristics of age, gender, and levels of education.

DISCUSSION

This study was carried out on the basis that common diagnostic radiologic procedures using ionizing radiation carry potential health risks; hence, patients' awareness and knowledge about ionizing radiation would play an important role in minimizing needless imaging and its ramifications. The results of our study in Bahrain show that awareness and knowledge of ionizing radiation are heterogeneous among prescribed patients and higher than the self-presented patients' confirming the hypothesis of this study.

Analyzing our study outcomes in detail, prescribed patients had a higher awareness of the minimum ionizing radiation permissible (85.0%) and preferred to undergo a clinical examination compared to a radiological procedure (67.0%). On the other hand, although significantly different to the self-presenting patients, it is of concern that the prescribed patient's awareness of the risks of ionizing radiation and their willingness to undergo the procedure even if harmful was below 50.0%. It is of serious concern to note that the awareness of self-presenting patients to ionizing radiation was poor since all their appropriate responses to awareness statements were below 10.0%. The results of our study closely mirrors one on the knowledge of radiation exposure in medical imaging in parents and legal guardians, who were largely unaware that medical imaging carries an inherent risk of exposure to radiation for their child.[19]

Only four out of 10 statements relating to knowledge had a statistically significantly higher proportion of appropriate responses in the prescribed category than the self-presenting category of patients. Of these four, only two statements (does radiological procedure offer best diagnoses than other medical tests or medical procedures, and can people prevent or minimize ionizing radiation?) had more than 50.0% appropriate responses. The proportion of appropriate response was below 50.0% for the questions, would preventing or minimizing ionizing radiation exposure improve a person's health, and is ionizing radiation a lifelong health concern? Among the patients who self-presented, the results were identical to their awareness responses and particularly worrying as their appropriate responses to knowledge statements were below 10.0% for nine out of 10 statements.

Although over 85.0% of patients were adults, 65.0% were university or high-school graduates, and 85.0% had a prior radiological procedure, their awareness and knowledge of ionizing radiation was inadequate, and no significant differences were found between age, gender, and education level.

The proportion of appropriate responses to awareness and knowledge were paltry for self-presenting patients and deficient for the prescribed patients in the knowledge segment. Thus, it must be construed that the Bahraini patients who reported to SMC lack awareness and knowledge on ionizing radiation, in particular, self-presenting patients. Other studies have also suggested that the exposure to ionizing radiation from medical procedures is not a concern to the general public. Patients probably trust that healthcare professionals are competent in minimizing any risks because of their comprehensive training in radiation protection.[20,21]

Public health care services are delivered free to all Bahraini nationals. Therefore, most often, self-presenting patients insist on radiological procedures and physicians are urged to oblige, or else patients may rate a care low when they perceive that their legitimate requests for a diagnostic radiological procedure was denied or ignored.[14] Additionally, they may seek a private practitioner to have it done.

Our work is not bereft of limitations. Firstly, this study was carried out only in SMC, so our sample refers to this specific population and may limit the generalizability of these findings to populations with access to other health care settings. Secondly, the population represented in our sample does not include pregnant women, those attending the accident and emergency department, and non-Bahraini patients, therefore, the results of our study could only be compared to similar patient populations. Thirdly, there is no standardized survey instrument available to assess awareness and knowledge of ionizing radiation, particularly in common diagnostic radiological procedures.

We utilized the existing literature and the opinion of experts in the field to design a data collection instrument that was comprehensive and detailed with an acceptable internal consistency. Fourthly, we did not attempt to create an overall index for the results of our data for a comparison between prescribed and self-presented patients as the data was not normally distributed, hence the median and interquartile range alone were presented. Further, we believed that each statement or question on awareness and knowledge provided necessary and sufficient information related to the aim of the study. Finally, the number of prescribed and self-presenting patients for common diagnostic radiological procedures is not equal since the patients were enrolled consecutively in the study and may serve as a surrogate of the prevailing proportion of self-presenting patients in the Bahraini population.

In recent years, improved recognition of the impacts of ionizing radiation has been identified as one of the major public health and medical challenges. Our findings suggest that a great need exists for health promotion in basic concepts of ionizing radiation exposure and risk in patients, caregivers, and the general population. Organizational efforts involving healthcare professionals should augment the public awareness and knowledge regarding diagnostic radiological procedures. A shared decision-making platform between healthcare professionals and patients offers the opportunity to discuss the benefits and risks associated with diagnostic radiological procedures.[22] Thereby, healthcare professionals become agents of public health in counseling on the risks and benefits of diagnostic radiological procedures and providing evidence-informed health care to their patients. To the best of our knowledge, this study is a first of its kind to assess the awareness and knowledge of ionizing radiation risks to patients for common diagnostic radiological procedures in Bahrain and, furthermore, on the comparison between prescribed and self-presenting patients. Further studies are required to assess the magnitude of the self-presenting patients including other health care settings in the country.

CONCLUSION

The Bahraini patients who reported to SMC lack awareness and knowledge on ionizing radiation. The appropriate responses to awareness and knowledge questions were paltry for self-presented patients and deficient in the prescribed patients in the knowledge segment. This study provides the first data on the differences in awareness and knowledge of ionizing radiation risks between prescribed and self-presenting patients for common diagnostic radiological procedures in Bahrain. Further studies are needed in diverse clinical settings among the population to validate our results and recommend a policy on exposure to ionizing radiation on common diagnostic radiological procedures. We strongly believe health promotion can play a significant role in preventing unnecessary ionizing radiation exposure to self-presenting patients, irrespective of their clinical condition.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

Acknowledgements

The authors would like to thank all the participants in the study, Mr. Amal Jacob of Christian Medical College, Vellore, India for valuable analytical inputs, and Mr. Mahdi AL Kulaiti, Chief of Radiology, SMC, Ministry of Health, Bahrain, for the support provided to carry out the study.

REFERENCES

1. Principles of ionizing radiation. In: Sam Keith, H. Edward Murray, Wayne Spoo, Chemical Managers/Authors, editors. Toxicological profile for ionizing radiation. U.S. department of health and human services. Public Health Service. Agency for Toxic Substances and Disease Registry. Atlanta, Georgia, USA: Agency for Toxic Substances and Disease Registry Division of Toxicology/Toxicology Information Branch; 1999. p.23-79.
2. Amis ES Jr, Butler PF, Applegate KE, Birnbaum SB, Brateman LF, Hevezi JM. et al; American College of Radiology. American College of Radiology white paper on radiation dose in medicine. J Am Coll Radiol 2007 May;4(5):272-284.
3. Berrington de González A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. Lancet 2004 Jan;363(9406):345-351.
4. Kempf SJ, Azimzadeh O, Atkinson MJ, Tapio S. Long-term effects of ionising radiation on the brain: cause for concern? Radiat Environ Biophys 2013 Mar;52(1):5-16.
5. International Commission on Radiological Protection (ICRP). Radiological Protection in Medicine. ICRP Publication 105. Ann. ICRP 37 (6). 2007 [cited 2016 September]. Available from: http://www.icrp.org/publication.asp?id=ICRP%20Publication%20105.
6. Preston RJ. Radiation biology: concepts for radiation protection. Health Phys 2005 Jun;88(6):545-556.
7. Scally AJ. Recommended standards for the routine performance testing of diagnostic X-Ray imaging systems. IPEM Report 91. York, UK: Institute of Physics and Engineering in Medicine. 2005 [cited 2016 August]. Available from: https://www.ipem.ac.uk/Publications/IPEMReportSeries/AvailablePublications.aspx.
8. Sierzenski PR, Linton OW, Amis ES Jr, Courtney DM, Larson PA, Mahesh M, et al. Applications of justification and optimization in medical imaging: examples of clinical

guidance for computed tomography use in emergency medicine. J Am Coll Radiol 2014 Jan;11(1):36-44.

9. International Atomic Energy Agency (IAEA). Report of a consultation on justification of patient exposures in medical imaging. Radiat Prot Dosimetry 2009 Jul;135(2):137-144.
10. Ford P. Understanding the issues involved in requesting X-rays. Nurs Times 2005 Oct;101(43):28-30.
11. Hadley JL, Agola J, Wong P. Potential impact of the American College of Radiology appropriateness criteria on CT for trauma. AJR Am J Roentgenol 2006 Apr;186(4):937-942.
12. Brenner DJ, Hall EJ. Computed tomography–an increasing source of radiation exposure. N Engl J Med 2007 Nov;357(22):2277-2284.
13. Malone J, Guleria R, Craven C, Horton P, Järvinen H, Mayo J, et al. Justification of diagnostic medical exposures: some practical issues. Report of an International Atomic Energy Agency Consultation. Br J Radiol 2012 May;85(1013):523-538.
14. Hofmann B, Lysdahl KB. Moral principles and medical practice: the role of patient autonomy in the extensive use of radiological services. J Med Ethics. 2008 Jun;34(6):446-449.
15. Kravitz RL, Bell RA, Azari R, Krupat E, Kelly-Reif S, Thom D. Request fulfillment in office practice: antecedents and relationship to outcomes. Med Care 2002 Jan;40(1):38-51.
16. Visiting Bahrain. About the Kingdom of Bahrain [cited 2016 October]. Available from: http://culture.gov.bh/en/visitingbahrain/about_bahrain/.
17. Kingdom of Bahrain. Ministry of Health. Our Services. Primary Health Care [cited 2016 September]. Available from: http://www.health.gov.bh/EN/MOHServices/Services/primaryHealthCare.aspx.
18. Arya R, Antonisamy B, Kumar S. Sample size estimation in prevalence studies. Indian J Pediatr 2012 Nov;79(11):1482-1488.
19. Hartwig HD, Clingenpeel J, Perkins AM, Rose W, Abdullah-Anyiwo J. Parental knowledge of radiation exposure in medical imaging used in the pediatric emergency department. Pediatr Emerg Care 2013 Jun;29(6):705-709.
20. Baerlocher MO, Detsky AS. Discussing radiation risks associated with CT scans with patients. JAMA 2010 Nov;304(19):2170-2171.
21. Arslanoğlu A, Bilgin S, Kubal Z, Ceyhan MN, Ilhan MN, Maral I. Doctors' and intern doctors' knowledge about patients' ionizing radiation exposure doses during common radiological examinations. Diagn Interv Radiol 2007 Jun;13(2):53-55.
22. Barrett TW, Rising KL, Bellolio MF, Hall MK, Brody A, Dodd KW, et al. The 2016 Academic Emergency Medicine Consensus Conference, "Shared Decision Making in the Emergency Department: Development of a Policy-relevant Patient-centered Research Agenda" Diagnostic Testing Breakout Session Report. Acad Emerg Med 2016 Dec;23(12):1354-1361.