Use of evidence-based medicine to choose contrast enhancing agents (iso-osmolar versus low-osmolar contrast media) for CT

Ping-Liang Chen  Yuan-Lin Lee  
Hui-Luu Zhan  Hung-Chih Lai*

Department of Radiology, Kuang Tien General Hospital

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Abstract

This article surveys academic publications and frameworks using evidence-based medicine (EBM) concepts. Contrast media are often used in diagnostic radiology. Contrast enhancement has been improved in recent years by switching from traditional high-osmolar ionic contrast media to low-osmolar non-ionic ones, and new agents with osmolarity similar to that of human body fluids have been developed. Currently, either high-osmolar or low-osmolar contrast media may be used clinically, hence contrast media need to be chosen and need to be discussed. This study evaluates studies on influence of iso-osmolar contrast medium on human kidneys and describes for radiological technologists the application of an EBM approach to literature evaluation. EBM should improve the quality of radiological examinations and the ability to choose the appropriate contrast medium.

Key words: Evidence-based medicine, non-ionic contrast medium, osmotic contrast agent, renal function
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1. Introduction

Contrast media are used to enhance the sensitivity and accuracy of medical diagnosis. The contrast medium is administered before imaging, but this may cause problems. The level of uncertainty is normally expressed as a probability, which may be estimated on the basis of personal experience or other evidence. Contrast media may cause allergic reactions and thereby affect the examination process.

Radiological technologists can use the results of objective and credible clinical studies to choose the safest contrast media for patients. Evidence-based medicine is a diagnostic paradigm that emphasizes the application of science-based, patient-centered approaches. The issue then is making clinical choices and how to apply them correctly in clinical practice, thereby improving the quality of radiological practice.

2. Materials and methods

Software and hardware are basic tools for the practical application of evidence-based medicine. Evidence-based medicine databases include CEPS (Chinese Electronic Periodical Services), Cochrane Library, MEDLINE, Pub Med, and other network resources such as medical journal sites. Web searching methods can be learned in the course of searching. One of the more important databases of evidence-based medicine, the Cochrane Library can reveal evidence-based clinical and medical decisions, reliable scientific references, and the latest information. Oxford Centre for Evidence Based Medicine categorizes clinical reports into levels of evidence (Level 1 to Level 4) based on study design framework. Evidence class is related to study design, and study design methods influence reliability of the evidence. At the highest level of evidence is the systematic review of randomized controlled trials (RCTs).

The five steps of EBM [1,2]:

Step 1 Ask questions

Formulate an answerable clinical question using clinical data and the four items of PICO (Patient Intervention Comparison Outcomes) to describe the clinical issue.

Step 2 Search for evidence [3]

Use the PICO framework to formulate the key words and strategy of each database search. Improper searching technique will affect the result and number of outcomes. Problems arising in database searching include spending too much time to find poor quality studies or stopping the search after finding only a few papers. Haynes recommends starting the search at the “5S level.” The 5S level has five levels: original studies (the first level), systematic review synthesis (second level), single studies or synopses of review articles (third level), summaries of certain clinical issues (fourth level), and EBM clinical information system (fifth level).

Step 3 Appraise the evidence

Before applying EBM theory, credibility, importance, and quality of evidence to support therapeutic value must be evaluated according to methods described on the Kuang Tien General Hospital website [1].

Step 4 Apply the evidence [3,4]
Ask yourself which evidence from the literature should be used together with clinical experience to make the best clinical decision.

*Step 5 Evaluate the outcome*

Evaluate whether EBM has been implemented correctly. Ask whether the efficacy and quality of this evaluation is adequate, and think of ways to improve the system of evaluation.

### 3. Results

**(1) Select basic information: case summary**

Ms Wu: 76 years old, hospitalized in April of 2009. History: Diabetes mellitus (DM) for 10 years; hypertension; headache, vomiting, weakness; abdominal discomfort, insomnia, myasthenia; high glutamate oxaloacetate transferase (GOT)/glutamate pyruvate transaminase (GPT). Blood urea nitrogen (BUN): 39 mg/dl; creatinine level: 3.5 mg/dl. Rule out (R/O) hepatoma: On the basis of the patient’s condition, confirmed in kidney function follow up, the doctor recommended performance of contrast-enhanced abdominal CT.

**(2) Using the five-step EBM method to evaluate potential treatments:**

(A) Ask questions

Question: How does the use of iso-osmolar contrast medium versus low-osmolar iodinated medium, used for contrast-enhancement of CT, affect kidney function?

Divide the question into PICO concepts: Patient: a 76-year-old woman with DM and hypertension; Intervention: low-osmolar contrast medium; Comparison: iso-osmolar contrast medium; Outcome: is it possible to reduce the rate of renal failure occurrence?

(B) Searching for evidence

Apply the PICO structure, design the search strategy, and select the appropriate vocabulary and synonyms in the different parts of the question before proceeding with the search. Enter the “Pub Med database.” Insert key word 【ionic-contrast medium versus nonionic-contrast medium】 【contrast-enhanced CT】 【renal function】 and limit search on the basis of topic, age, gender, English literature, or journal. Three articles were found. Two of the three were published in 1993 and 1991 [5], respectively. These references were excluded because the patients described and our patient differed in age; also these were case reports, and the opinions expressed were unclear. The third was a review article published in 2006 entitled “Contrast medium use” [6, 7]. The review was current and could provide the latest information. Continuation of the search revealed that the data were not from randomized controlled trials (RCTs) but rather from case controlled studies and therefore of low reliability. Therefore, this article was also excluded.

Unable to find the appropriate articles using the Pub Med database, we searched the Cochrane Library database using the same key words [8] and found 20 articles, which were published between 1998 and 2007. Most were case reports and expressed no clear or exact expert opinions, and some did not evaluate RCT data. Therefore, they were excluded as references. Only one article (published in the journal “Radiology” in 2008) described a randomized controlled study, which
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was a double-blind randomized single controlled trial (RCT-1b) with statistical significance, a clearly described sampling procedure, and sufficient follow-up time (90 days) [9]. This article qualified for inclusion based on the above-mentioned EBM conditions. A flowchart in the report showed that 267 of 393 patients had to be excluded on the basis of the criterion <1.5. The remaining 126 patients were included. The iso-osmolar contrast medium iodixanol was used in 65 cases. Only 64 patients were included for follow up inasmuch as one patient was excluded for undisclosed reasons. The low-osmolar contrast medium iopromide was used in 61 cases. Only 56 were included for follow up, and 5 were excluded for undisclosed reasons. Patients in this study were randomly assigned to receive one of the two contrast media.

There were no significant between-group differences in age, gender, race, body weight, source of patients, serum creatinine (SCr) level, glomerular filtration rate (GFR), etc. (P < 0.05), indicating the two groups had almost the same characteristics. Therefore, the study was considered reliable as a reference. The between-group difference in SCr level was greatest one day after contrast agent administration, and SCr level was significantly lower in the group receiving the iso-osmolar contrast medium iodixanol (Fig. 1-A). SCr level increased 0.5 mg/dl or 1 mg/dl or more (Fig. 1-B). SCr level increased 25–50% after iodixanol, and increased even more after iopromide (Fig. 2-A). These increases were statistically significant (P <0.05; Fig. 2-B), indicating that adverse effects of iodixanol injection on kidney function in high risk patients were less. Figure 3 shows that administration of massive amounts of saline and renal protective agents before the injection of iodixanol or iopromide reduces GFR by 0.5 mg/dl or more. Figure 4 shows that the changes in SCr level and GFR were not statistically significant (P>0.05) because there were only eight participants. Nevertheless, it is obvious that iodixanol had a less adverse effect. Figure 5 shows no significant difference in the change of SCr level and change in GFR due to injection of contrast agent (iodixanol or iopromide) between patients with DM and without DM (P>0.05). This part of the study had no meaning.

Figure 6 shows a very low rate of permanent adverse reactions to injection of iopromide in all participants. Taken together, the results of this study indicate that injection of iodixanol (compared with iopromide) led to a smaller change in SCr level.

(3) Critical appraisal [1]

Table 1 presents the evaluation.

(4) Evidence application [1,2,10]

1. Are characteristics of your patients similar to those of patients in the study? If so, its results can be applied.

Yes. Age, basic history, and the use of contrast media were similar in our patients and the patients in the study. Therefore, the EBM study results could be applied to our patients.

2. Do you expect your patients to benefit from the study results?

Yes. The EBM study provided knowledge needed for selecting the contrast medium with the lowest risk of renal impairment.

3. Are the study results applicable to your patients?
Yes. The results enabled us to choose the appropriate contrast medium and to be aware of their associated risks.

**5. Outcome Evaluation**

1. Are you recording your questions?

Yes. A “special X-ray examination check list” was filled out for every patient who required injection of contrast medium for medical record and medical data collection purposes.

2. Are you looking for additional evidence from outside resources?

Yes. Electronic journal databases were searched to obtain the latest news, and data were solicited from the suppliers of the contrast media.

3. Is the speed of your searches and evidence evaluation fast or slow?

Slow. The main reason was lack of acquaintance with certain medical terms.

4. Can you apply information from evidence based sources to patients?

Yes. EBM information on the health effects of contrast media could be explained to patients.

**4. Conclusions**

From this follow-up study, it can be concluded that (compared to low-osmolar contrast medium) iso-osmolar contrast medium causes less change in SCr level and less renal damage. It is hoped that the National Health Insurance will one day reimburse patients charged for iso-osmolar contrast medium so as to improve the quality radiological services. This evidence-based study of the medical literature encourages radiological technologists to raise questions concerning improving medical techniques, quality of care, and habits of acquiring new information. They can learn how to search for clinical reports and to incorporate new knowledge into clinical practice and provide patients with better quality information and services. Moreover, I now understand the importance of evidence-based medicine.

**5. Acknowledgment**

We thank Chun-hua Ka, MD, Dr. Wen-an Lai, MD, and Yu-cheng Haung, RN, for their valuable opinions and guidance in this study.

**References**

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![Graph A](image1)

**A**

SCr level on day 1 after CT was significantly lower than baseline iodixanol group ($P < 0.05$) SCr level on day 1 after CT in iodixanol group was significantly lower than in iopromide group ($P < 0.05$)

![Graph B](image2)

**B**

Incidence of SCr level increase of $0 \div 5$ mg/dl or $>0 \div 10$ mg/dl or more for patients receiving iodixanol (black) and iopromide (gray) $* = P < 0.05$

Fig. 1 During a three-day follow-up period, incidence of SCr level elevation of more than 25% or more than 50%.

(From, Shaun A, Radiology, 2008; 248:97-105, 2011)
In conclusion

The incidence of contrast medium–related permanent adverse outcomes with intravenous application of current iodinated contrast media in high-risk patients is low; SCR levels after contrast medium administration are lower when iso-osmolarity ioxaglate is used as compared with low-osmolarity iopromide.

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Fig 2 Incidence of SCR level $\geq 25\%$ or $\geq 50\%$
(From, Shaun A, Radiology, 2008;248:97-105, 2011)

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Fig 3 Change of GFR in three days/ Incidence of GFR level
(From, Shaun A, Radiology, 2008;248:97-105, 2011)
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Fig 4 SCr level and GFR changes over a three-day follow-up period.

(From, Shaun A, Radiology, 2008; 248:97-105, 2011)

Fig 5 SCr level and GFR changes in the two groups.

(From, Shaun A, Radiology, 2008; 248:97-105, 2011)
In conclusion

The incidence of contrast medium-related permanent adverse outcomes with intravenous application of current iodinated contrast media in high-risk patients is low; SCr levels after contrast medium administration are lower when iso-osmolality ioxpanol is used, as compared

Table 1  Results of the evaluation.

<table>
<thead>
<tr>
<th>Question</th>
<th>YES or NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Were there clearly defined groups of patients, similar in all important ways other than exposure to the treatment or other cause?</td>
<td>YES</td>
</tr>
<tr>
<td>2. Were treatments/exposures and clinical outcomes measured in the same ways in both groups (was the assessment of outcomes either objective or blinded to exposure)?</td>
<td>YES</td>
</tr>
<tr>
<td>3. Was the follow-up of study patients complete and long enough?</td>
<td>YES</td>
</tr>
<tr>
<td>4. Do the results satisfy some “diagnostic tests for causation”?</td>
<td>YES</td>
</tr>
<tr>
<td>5. Is it clear that the exposure preceded the onset of the outcome?</td>
<td>YES</td>
</tr>
<tr>
<td>6. Is there a dose-response gradient?</td>
<td>YES</td>
</tr>
<tr>
<td>7. Is there positive evidence from a “dechallenge-rechallenge” study?</td>
<td>NO</td>
</tr>
<tr>
<td>8. Is the association consistent from study to study?</td>
<td>YES</td>
</tr>
<tr>
<td>9. Does the association make biological sense?</td>
<td>YES</td>
</tr>
</tbody>
</table>

Fig 6 Patient outcomes
(From, Shaun A, Radiology, 2008; 248:97-105, 2011)
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以實證醫學探討低滲透性與等滲透性顯影劑對腎臟功能的影響

陳平涼  李垣林  詹慧倫  賴鴻池*

光田醫療法人光田綜合醫院大甲院區  放射診斷科

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摘要

本文以實證醫學(evidence-based medicine，EBM)分析學術論著及其架構為基礎，以放射診斷科常用顯影劑為主題，從一開始高滲透性傳統離子顯影劑改善為低滲透性的非離子顯影劑，近幾年來更進一步發展出滲透壓與人體體液相似的等滲透性顯影劑，但現在一般臨床上仍然以使用高滲透性或低滲透性傳統離子顯影劑占較大多數，因此顯影劑的選擇是需要一再地被改善及探討的問題。此研究利用了解等滲透性顯影劑對人體腎臟功能有多少程度的影響，讓臨床放射師人員在實際應用時更有參考依據，進一步能夠提升放射科的用藥及檢查品質。

關鍵詞：實證醫學、非離子顯影劑、滲透性顯影劑、腎臟功能

*通訊作者：賴鴻池

437臺中市大甲區經國路321號 光田醫療法人光田綜合醫院大甲院區--放射診斷科
電話：037-759999轉166    E-mail：liang-1976@yahoo.com.tw