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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Intraosseous Contrast Media Injection for Computed Tomography Scan or Magnetic Resonance Imaging: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

CT	computed tomography
IO	intraosseous
IV	intravenous
MRI	magnetic resonance imaging
NRS	non-randomised study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Context and Policy Issues

Contrast agents are often used in computed tomography (CT) and magnetic resonance imaging (MRI) to help delineate borders between tissues with similar radiodensity.[1] Administration of these agents is usually performed through an intravenous (IV) route;[1] however, the ability to find a suitable venous access site and successfully complete cannulation (i.e., the insertion of a tube for fluid delivery or extraction) is not always possible (e.g., cases of severe hemorrhage, dehydration, burns, obesity, chronic IV drug use).[2-4] The intraosseous (IO) route offers an alternative, as the veins in the bone marrow of long bones do not collapse in patients with shock.[3] Once the contrast media enters venous circulation via this route, it will distribute systemically, as it would with the IV route. Typical locations for IO cannulation include the proximal tibia, the distal femur, the distal tibia or fibula, the proximal humerus, and the manubrium.[3]

As with any drug, contrast agents have side effects, regardless of the route of administration, which can vary depending on the agent's ingredients. These include allergic-type reactions, renal damage (i.e., contrast nephropathy), and contrast media extravasation.[1,2,4] Furthermore, there are complications specific to the IO route (e.g., bone fractures,[3] osteomyelitis [bone infection],[2,3] fat and bone marrow emboli,[2,3] and other infections[2]).

Previous CADTH reports on this topic include a 2015 Summary of Abstracts on the securement devices for intraosseous needles,[5] a 2010 Summary of Abstracts on intraosseous infusions for patients needing emergency fluid resuscitation,[6] and a 2009 report on the clinical effectiveness and cost-effectiveness of intraosseous insertion devices.[7] The objective of the present report is to investigate the comparative clinical effectiveness of IO contrast media injection versus IV contrast media injection for patients undergoing CT scan or MRI.

Research Questions

1. What is the comparative clinical effectiveness of intraosseous contrast media injection versus intravenous contrast media injection for patients undergoing computed tomography scan or magnetic resonance imaging?
2. What are the evidence-based guidelines regarding the use of intraosseous contrast media injection for patients undergoing computed tomography scan or magnetic resonance imaging?

Key Findings

One relevant non-randomized study was identified regarding the comparative clinical effectiveness of intraosseous contrast media injection versus intravenous contrast media

injection for patients undergoing computed tomography scan. No relevant evidence-based guidelines were identified.

Although the study found no difference in objective and subjective computed tomography image quality between intraosseous and intravenous contrast media delivery, it remains uncertain whether the findings are reliable given that the study was likely not adequately powered nor reflective of the larger clinical population.

The limitations of the included study, such as lack of blinding to treatment, inadequate comprehensiveness of post-interventional complications reporting, small sample size, and disproportionate gender balance, should be considered when interpreting the results.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were intraosseous or intravenous contrast media injections and computed tomography scan or magnetic resonance imaging. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, any types of clinical trials or observational studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and January 10, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Acutely ill patients (of any age)
Intervention	CT scan or MRI performed using intraosseous contrast media injection
Comparators	Q1: CT scan or MRI performed using intravenous contrast media injection Q2: No comparator required
Outcomes	Q1: Clinical effectiveness (e.g., safety [e.g., rates of adverse events]) Q2: Evidence-based guidance and recommendations (e.g., scanning protocols)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

CT = computed tomography; MRI = magnetic resonance imaging.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015.

Critical Appraisal of Individual Studies

The included non-randomised study (NRS) was critically appraised using the Downs and Black checklist.[8] Summary scores were not calculated; rather, a review of strengths and limitations of the included study was described narratively.

Summary of Evidence

Quantity of Research Available

A total of 295 citations were identified in the literature search. Following screening of titles and abstracts, 270 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. No additional potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 24 publications were excluded for various reasons, and one publication met the inclusion criteria and were included in this report. These comprised one non-randomized study (NRS). Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[9] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

One NRS was identified and included in this review.[10] No relevant health technology assessments, systematic reviews, randomized controlled trials, or evidence-based guidelines were identified. Detailed characteristics are available in Appendix 2, Table 2.

Study Design

One primary study, a 2019 retrospective case-control study, regarding the clinical effectiveness of IO contrast media injection for emergency CT was identified.[10]

Country of Origin

The NRS was conducted in Germany.[10]

Patient Population

The NRS evaluated 24 patients who underwent emergency CT as part of their management at a trauma centre emergency department.[10] Four patients (cases) were identified as having received tibial IO access because of failed IV access.[10] These were matched to twenty consecutive patients (controls) of similar age and heart rate characteristics.[10] Case patients in the IO arm were predominantly males (n = 3), with a mean age of 57.0 years.[10] Similarly, those in the control arm were predominantly males (n = 17), with a mean age of 58.8 years.[10] Both groups received identical trauma CT protocols and the same amount of iodinated non-ionic contrast media.[10]

Interventions and Comparators

The NRS compared tibial intraosseous (IO) access with intravenous (IV) access for contrast media injection prior to emergency CT of the head (including cerebral CT angiography), chest (including supra-aortic vasculature CT angiography), abdomen, and if required, the lower limbs.[10]

Outcomes

In the NRS, the outcomes of interest were objective and subjective image quality.[10] Image quality is essential in radiology in order to obtain the optimal diagnostic image at the lowest possible radiation dose.[11] In this study, objective image quality was evaluated by measuring the contrast-to-noise ratio (a measure of the degradation of contrast)[11], the absolute attenuation (the reduction of the intensity in the beam as it goes through matter)[12], and image noise (the standard deviation of absolute attenuation (measured in Hounsfield Units [HU]).[10]

Subjective image quality was evaluated independently by three radiologists, who graded image noise (minimal, slight, strong, or extremely strong image noise), delineation of vascular structures (in three regions of interest, using a four point scale), and overall image quality (also using a four point scale: very good, good, limited, or insufficient).[10]

Complications (e.g., extravasation, fatty embolisms, osteomyelitis) in the IO group were also evaluated.[10]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 3.

The NRS had several strengths, such as: clear descriptions of objectives, interventions, main outcomes, population characteristics, eligibility criteria; no patients were lost to follow up; and main outcome measures used were valid and reliable.[10] However, the study was open-label with no blinding of outcome assessors.[10] This may have introduced an observation bias (in either direction) in the interpretation of the effect. Authors did not report conducting an a priori power calculation;[10] therefore, it is uncertain if the sample size was adequate to detect statistically significant differences between the groups. Although authors reported on post-interventional complications, there is uncertainty as to the reliability of these findings since the study may not have been adequately powered to investigate this outcome. Furthermore, the study did not report on the length of follow up post-intervention;[10] therefore, it is unclear if it was adequate to examine delayed clinical events. Also, authors did not report on additional confounding factors that could affect computed tomography image quality, such as: fat content, scan time, or slice thickness.

Summary of Findings

A detailed summary of findings and recommendations is provided in Appendix 4, Table 4.

Comparative clinical effectiveness of intraosseous contrast media injection versus intravenous contrast media injection for patients undergoing computed tomography scan or magnetic resonance imaging

Complications

For the IO group, authors of the study reported that no access-related, or CT-related, complications occurred during or after the scan.[10] The study did not report on any IV related complications.[10]

Image Quality

There were no statistically significant between-group differences in the following objective image quality parameters and regions of interest: absolute CT-attenuation of the head/neck, chest, and abdomen (respective *P* values = 0.398, 0.911, 0.454); image noise of the head/neck, chest, and abdomen (respective *P* values = 0.421, 0.364, 0.807); and contrast-to-noise ratio of the head/neck, chest, and abdomen (respective *P* values = 0.860, 0.494, 0.687).[10]

Similarly, the authors reported no statistically significant between-group differences in the following subjective image quality parameters: delineation of all evaluated vessels (*P* value = 0.405), and overall image quality (*P* value = 0.196).[10]

Evidence-based guidelines regarding the use of intraosseous contrast media injection for patients undergoing computed tomography scan or magnetic resonance imaging

No relevant evidence regarding the use of IO contrast media for patients undergoing CT or magnetic resonance imaging (MRI) was identified; therefore, no summary can be provided.

Limitations

A number of limitations were identified in the critical appraisal as shown in Appendix 3, Table 3; however, additional limitations exist. The main limitations of this review are related to limited size of the study population, inadequate comprehensiveness of post-interventional complications reporting, and generalisability of findings.

An additional limitation that should be considered when interpreting these results is that the relevant study was of case-control design,[10] with associated methodological limitations (e.g., selection bias, cannot determine causality).

Authors reported on CT or IO related complications but did not compare the complication rates between IO and IV access routes,[10] which prevents a comprehensive comparison of clinical safety. This suggests that additional comparative research in this area is required.

The ability to generalise conclusions from this study is uncertain, as the study had four IO participants and it is unlikely that they were reflective of all patients who may be considered for IO access. Also, the study looked at imaging results in specific anatomical regions of interest and it may be difficult to generalise the results to other regions.

Lastly, it may be difficult to generalise the results in women since the study enrolled a disproportionately higher number of men.[10]

Conclusions and Implications for Decision or Policy Making

This report identified comparative clinical effectiveness evidence regarding the use of IO versus IV contrast media for patients undergoing CT scan or MRI. No relevant evidence-based guidelines were identified.

The identified study suggested that CT image quality for select regions of interest,[10] is no different when using an IO delivery route than with an IV delivery route for absolute CT-attenuation, image noise, contrast-to-noise ratio, delineation of all evaluated vessels, and overall image quality parameters. No complications in the IO group were identified. These findings should be interpreted cautiously, as it is unclear if the study was adequately powered to detect differences for any outcome.

A study evaluating patients receiving IO contrast media delivery for an alternative imaging intervention (ultrasound imaging) was also identified from the literature search for this Rapid Response report. Similar to the included study in this report, it had a small sample size (n = 10) and limited findings on IO related complications.[13] This suggests that comparative effectiveness and safety of IO versus IV is not well established.

The limitations of the included study in this report should be considered when interpreting the results. The findings highlighted in this review come with a high degree of uncertainty. Further research investigating the comparative clinical effectiveness of contrast media administration via IO and IV routes, especially by way of large, methodologically sound randomized controlled trial would help reduce this uncertainty.

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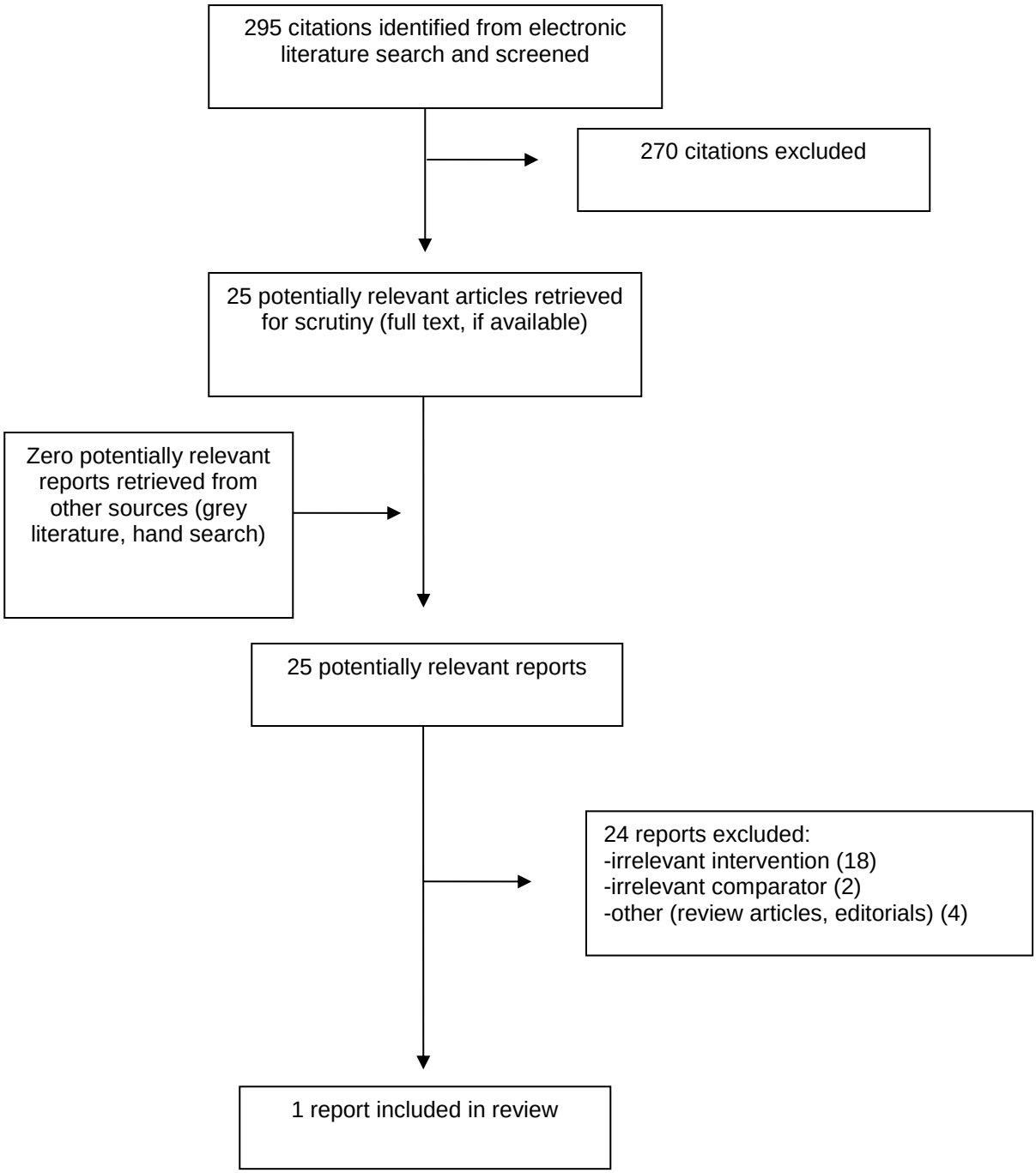
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Non-Randomized Studies				
Schindler, 2019[10] **Germany**	**Study design**: retrospective case-control study **Setting**: a trauma centre emergency department **Objective**: feasibility study comparing IO versus IV contrast media injection for emergency CT	Patients who underwent emergency CT as part of trauma management **Number of patients**: • IO n=4 • IV n=20 **Mean age, years (± SD):** • IO: 57.0 ±1 1.0 • IV: 58.8 ± 4.4 **Sex**: • IO: 3 males • IV: 17 males	**Intervention**: tibial IO access **Comparator**: peripheral IV access	**Outcomes**: - Objective image quality - Subjective image quality **Follow-up**: NR

CT = computed tomography; IO = intraosseous; IV = intravenous; NR = not reported; SD = standard deviation.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black[8]

Strengths	Limitations
Non-Randomized Studies	
Schindler, 2019[10] Germany	
• The study's objective, intervention, and main outcomes were clearly described • Population characteristics were clearly described, and eligibility criteria given • The major findings of the study were described in a way that allows verification of analyses and conclusions • Estimates of random variability were reported • Data analyses were planned at the outset • No patients were lost to follow up • Actual probability values were reported • Sources of funding were disclosed (no specific funding) • Conflicts of interest were disclosed (none)	• This was an open-label study with no blinding of study participants or outcome assessors. This may have introduced a bias in the interpretation of the results • The time period over which patients were recruited was not specified; therefore, the introduction of a selection bias cannot be assessed • Length of follow up was not specified. This introduces uncertainty with regards to the measurement of post-intervention complications • This study had no sample size calculations to determine the ideal patient number needed to detect a clinically important effect. The low patient number (n = 4) in the intervention group may denote that it was underpowered • It is uncertain if these German findings are generalizable to the Canadian setting. Also, the study's setting (emergency department of a trauma centre), introduces uncertainty regarding the generalizability of the results in tertiary-level care hospitals or non-emergency care • Authors did not discuss other factors that could affect computed tomography image quality, such as fat content, scan time, slice thickness

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Non-Randomized Studies	
Schindler, 2019[10] Germany	
Complications Intraosseous: • no IO access-related, or CT-related, complications during of after the scan. Intravenous: • NR **Objective image quality** Intraosseous (n=4): 1) Absolute CT-attenuation (mean HU ± SD): a. Head/neck: 303.1 ± 184.7 b. Chest: 200.0 ± 62.4 c. Abdomen: 201.5 ± 69.0 2) Image noise (mean SD of HU): a. Head/neck: 20.0 ± 11.5 b. Chest: 13.7 ± 1.4 c. Abdomen: 21.3 ± 3.8 3) CNR (mean ratio HU/noise): a. Head/neck: 28.7 ± 19.1 b. Chest: 19.3 ± 4.0 c. Abdomen: 13.3 ± 5.5 Intravenous (n=20): 1) Absolute CT-attenuation (mean HU ± SD): a. Head/neck: 359.4 ± 105.4 b. Chest: 197.7 ± 28.5 c. Abdomen: 183.8 ± 32.3 2) Image noise (mean SD of HU): a. Head/neck: 30.5 ± 25.0 b. Chest: 15.3 ± 3.0 c. Abdomen: 22.0 ± 4.2 3) CNR (mean ratio HU/noise): a. Head/neck: 26.7 ± 20.1 b. Chest: 17.8 ± 3.3 c. Abdomen: 12.5 ± 2.8 Between-group P-values: 1) Absolute CT-attenuation: a. Head/neck: 0.398 b. Chest: 0.911 c. Abdomen: 0.454 2) Image noise: a. Head/neck: 0.421 b. Chest: 0.364 c. Abdomen: 0.807 3) CNR: a. Head/neck: 0.860 b. Chest: 0.494 c. Abdomen: 0.687	"We demonstrated that [IO] CMI could be performed using established CT protocols with identical contrast medium amount and flow rate comparable to [IV] CMI. Here, no complications were observed. In all examinations we obtained a good to very good image quality of the chest and abdomen comparable and without significant difference to [IV] CMI."[10] (*p*6)

Main Study Findings	Authors' Conclusion
Subjective image quality Intraosseous (n=30 images): 1) Subjective image noise: a. Minimal, n=13 (43.3%) b. Slight, n=14 (46.7%) c. Strong, n=3 (10%) 2) Delineation of all evaluated vessels: a. Median score 1.0, mean 1.2 ± 0.4 3) Overall image quality: a. Median score 2.0, mean 1.75 ± 0.45 Intravenous (n=180 images): 1) Subjective image noise: a. Minimal, n=58 (32.2%) b. Slight, n=111 (61.7%) c. Strong, n=11 (6.1%) 2) Delineation of all evaluated vessels: a. Median score 1.0, mean 1.1 ± 0.3 3) Overall image quality: a. Median score 1.5, mean 1.52 ± 0.54 Between-group P-values: 1) Subjective image noise: a. NR 2) Delineation of all evaluated vessels: a. 0.405 3) Overall image quality: a. 0.196	

CMI = contrast media injection; CNR = contrast-to-noise ratio; CT = computed tomography; HU = Hounsfield Units; IO = intraosseous; IV = intravenous; NR = not reported; SD = standard deviation.

Appendix 5: Additional References of Potential Interest

Alternative Intervention – Ultrasound Imaging

Cho Y, You Y, Park JS, et al. Comparison of right and left ventricular enhancement times using a microbubble contrast agent between proximal humeral intraosseous access and brachial intravenous access during cardiopulmonary resuscitation in adults. *Resuscitation*. 2018 Aug;129:90-93.
PubMed: PM29928956

Case Reports

Winkler M, Issa M, Lowry C, Chornenkyy Y, Sorrell V. Intraarticular extravasation, an unusual complication of computed tomographic angiography performed with intraosseous needle intravenous access. *Cardiovascular diagnosis and therapy*. 2018 Aug;8(4):516-519.
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Budach NM, Niehues SM. CT angiography of the chest and abdomen in an emergency patient via humeral intraosseous access. *Emergency radiology*. 2017 Feb;24(1):105-108.
PubMed: PM27572932