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TITLE: Methodological characteristics of randomized controlled trials of ultrasonography in emergency medicine: a review

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RUNNING TITLE: Methodological characteristics of randomized controlled trials of ultrasonography

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ABSTRACT

Introduction: Interest in ultrasonography in emergency medicine has increased in recent years, as reflected by a marked increase in publications on the topic. The aim of this study was to 1) describe and evaluate methodological characteristics of randomized controlled trials (RCTs) evaluating an ultrasound intervention in emergency department and 2) estimate whether the reports adequately described the intervention to allow replication.

Methods: We searched MEDLINE via PubMed for RCTs published in 2015 assessing an ultrasound intervention, regardless of type, that were performed in an emergency department or evaluated in an emergency situation. Two researchers independently screened titles, abstracts and full texts. Data from all included studies were independently extracted. The Cochrane Collaboration Risk of Bias tool was used to assess risk of bias of reports, and the intervention reporting was evaluated by using the Template for Intervention Description and Replication checklist.

Results: We identified 11 reports. The most frequent topic was vascular access/identification (n=4). Random sequence generation and allocation concealment were performed correctly in 55% and 27% trials. Three quarters of reports (73%) showed improper reporting or absence of participant blinding. Risk of bias due to assessor blinding was rated low for 3 RCTs (27%), risk of attrition bias low for all reports, and risk of selective outcome reporting unclear for most reports (n=10). Only 3 reports (27%) provided an optimal description of the intervention.

Conclusion: The quality of these trials raises questions. In our sample, the authors did not correctly report blinding of participants and assessors or allocation concealment

1. INTRODUCTION

Interest in ultrasonography (US) in emergency medicine has increased in recent years, as reflected by a marked increase in publications on the topic [1]. Recent years have seen calls for an increase in emergency ultrasound research and manuscript publication to provide additional evidence of clinical efficacy [2-3]. In fact, mounting clinical evidence documents the value of point-of-care US as an important diagnostic, clinical-management, and procedural tool that results in improved patient safety and quality of care [4-5]. The number of guidelines for using US in emergency departments (EDs) has increased greatly [6-7].

With the interest in US in emergency medicine, determining whether trials with published results are well-designed, transparent and fully reported could be useful to clinicians. Poor reporting does not necessarily mean poor methods [8], but adequate reporting allows readers to assess the strength and weakness of published studies and improve the replication of interventions in daily practice [9-10].

To our knowledge, the methodological characteristics of randomized controlled trials (RCTs) of US in emergency medicine have not been assessed. The aim of this study was to 1) describe and evaluate the methodological characteristics of trials evaluating an ultrasound intervention in an ED and 2) estimate whether the reports adequately described the intervention to allow replication in practice.

2. METHODS

2.1 Study design

We performed a review of RCTs assessing an ultrasound intervention in emergency medicine that were published over a 1-year period. We used the Cochrane Collaboration Risk of Bias tool [11] to assess the risk of bias of included RCTs. We report this systematic review in accordance with the Preferred Reporting of Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [12].

2.2 Search strategy and study selection

We searched MEDLINE via PubMed for RCTs in English, first published from January 1, 2015 to December 31, 2015 (search date: January 10, 2017) by using a combination of text words and MeSH terms. The search strategy is in Appendix 1. We included all RCTs assessing an ultrasound intervention, regardless of type, in an ED or evaluating an emergency situation. We excluded systematic reviews or meta-analyses, methodological publications, editorials, research letters, secondary analysis, abstracts or posters, correspondence, and protocols. Two reviewers (QD and EH) independently examined all retained citations based on the title and abstracts, then the full text of relevant studies according to inclusion and exclusion criteria. Any discrepancies were resolved by discussion with a third researcher (AC).

2.3 Data extraction

Two independent reviewers (QD and AC) extracted data by using a standardized data extraction form. Any discrepancies were discussed to reach consensus. If needed, a third reviewer (YY) was consulted.

2.4 General characteristics of RCTs

For each RCT, we assessed the following:

- 1) General characteristics: name of journal, year of publication, location of studies, publication delay, single-center study or multi-center study, the reason of the US, number of participants randomized and analyzed, type of participants performing the procedure (e.g., nurses, medical students), study design, ethical committee approval, reporting of registration number or study protocol available.
- 2) Primary outcomes: we extracted primary outcomes as defined in the report. If the primary outcome was unclear, we used the outcome stated in the sample size calculation.
- 3) Type of comparator (e.g., usual procedure or not) and the tested intervention.

2.5 Risk of bias assessment

The risk of bias in each RCT was evaluated by assessing the following key domains of the Cochrane Collaboration Risk of Bias tool [11]: selection bias (i.e., methods for random sequence generation and allocation concealment), performance bias (i.e., blinding of participants and personnel), detection bias (i.e., blinding of outcome assessors), attrition bias (i.e., incomplete outcome data), and reporting bias (i.e., selective outcomes reporting). Each domain was rated at low, high, or unclear risk of bias by the Cochrane handbook recommendations [13].

2.6 Reproducibility

We used the Template for Intervention Description and Replication (TIDieR) to formulate and guide assessments of key methodological components in reports [10]: what materials (i.e., describe physical or informational materials used in the intervention), what procedures (i.e., describe each

step of the procedures), who provided (i.e., description of intervention provider), where (i.e., describe the type[s] of location[s]), when and how much (i.e., report the number of times the intervention was delivered), how well planned (i.e., if intervention adherence was assessed, how and by whom, and any strategies to maintain or improve adherence) and how well delivered (actual) (i.e., assessment of intervention adherence delivery as planned). Complete descriptions are in Table 1.

2.7 Data and statistical analysis

We reported normally distributed continuous variables as means with SD or as medians with the first and third quartiles (Q1–Q3) and discrete variables as counts or proportions. For risk of bias defined by the Cochrane Collaboration, we determined the frequency of the presence of each bias item. SAS 9.3 (SAS Inst. Inc., Cary, NC, USA) was used for all analyses.

3. RESULTS

3.1 Search results

We identified 1406 reports of RCTs; 799 reports described research of an ultrasound intervention. Only 11 reports were in the emergency medicine field (Figure 1).

3.2 General characteristics

We identified 11 reports of RCTs published in 7 different journals. Most were published in emergency medicine journals (n=7; 63%). North America were the most frequent location of the studies (n=7; 64%). All studies were single-center study (n=11). Almost all had ethical committee approval (n=9; 82%). Only one study was registered.

Half of the studies evaluated an educational intervention (i.e., to identify vascular access) and half a clinical intervention. The median number of ultrasound operators was 36 [IQR 16-65] (Table 1). Four studies did not provide the number of operators included in the study. The most frequently studied operators were medical students or resident physicians (n=4 reports), emergency physicians (n=2) or both (n=1).

Reason for the US (Appendix 1)

Vascular access or identification – One third of studies examined vascular access (n=2) [14-15] or vascular tracking (n=2) [16-17]. The study population was medical students (n=2), medical residents (n=1) or nurses (n=1). Trials involved patients or volunteers (n=3) or a simulator (n=1). The most frequent comparator was the usual procedure (n=3). Outcomes were various.

Dyspnea – Three RCTs studied the contribution of US in dyspnea management in emergency situations: two evaluated its contribution to diagnosis [18-19] and one monitoring non-invasive ventilation [20]. The study population was medical students (n=1), emergency physicians (n=1) or

both (n=1). All interventions involved patients in EDs. The usual process was the comparator in all studies. Diagnosis was the most frequent outcome (n=2).

Focused Assessment with Sonography for Trauma (FAST) – Two studies evaluated the FAST procedure [21-22]. The study population was emergency students or a pre-hospital team. The usual process was the comparator in both studies. Outcomes were FAST image acquisition and interpretation skills assessment scores or a composite (comparison of ultrasound knowledge, comfort with use of US and results of an objective structured clinical examination).

Others – The remaining RCTs (n=2) focused on ultrasound-guided nerve blocks [23] or contrast-enhanced US in placing an endovascular balloon in the aorta [24].

3.3 Risk of bias assessment

We rated 6 (55%) and 3 (27%) RCTs at low risk of bias for random sequence generation and allocation concealment (Table 2); 8 (73%) at unclear or high risk of bias for improper reporting or absence of participant blinding; and 2 (27%) at low risk of bias for assessor blinding. We rated all RCTs at low risk of bias for attrition bias. Because trials were mostly unregistered, the risk of selective outcome reporting was unclear in most reports (n=10, 91%).

3.4 Reproducibility

Only 3 articles (27%) correctly reported all the items of the modified TIDieR checklist for intervention descriptions (Appendix 2). The items “where” and “what procedure” were provided in all studies (n=11). Only one study did not report any materials used. Three-quarters of reports (n=8; 73%) reported “who” provided the intervention; however, authors failed to report the background of participants and/or the number of participants providing the intervention. The

“when” and “how much” items were completely reported for 4 studies (36%). Authors failed to report the number of times the intervention was delivered and their duration. Adherence (planned and actual) to the intervention was correctly reported in only 3 (27%) and 1 (9%) articles.

ACCEPTED MANUSCRIPT

4. DISCUSSION

We performed a review of methodology for published RCTs assessing an ultrasound intervention in emergency medicine. Results of only 11 RCTs were published during 2015; RCTs represented a small part of the research in ultrasound intervention. The most frequent topics were vascular access and dyspnea. Only 3 RCTs had low risk of bias for performance and detection bias (blinding of outcome assessors). One quarter correctly reported all the items of the modified TIDieR checklist for intervention descriptions.

Although many emergency physicians are convinced of the use of US in patient care, few studies with a high methodological quality have been performed [25]. In 2016, Bayram *et al.*, published a bibliometric analysis of the top 100 most-cited clinical studies of US in EDs [26]: between 1988 and 2010, 85 had a prospective cohort design, 6 were retrospective studies and only 9 were RCTs. The weight of RCTs in the emergency US literature remains low.

Several analyses evaluated the methodology in studies of specific ultrasound topics [27-30]. Many highlighted limits of internal validity linked to the lack of blinding. In fact, blinding patients or participants to the intervention seems impossible and studies are at increased risk of performance bias. However, some strategies exist for limiting this risk of bias. For example, Ueda *et al.* [31] compared the utility of two different radial arterial cannulation techniques in pediatric patients: US-guided versus Doppler-assisted technique. To ensure the blinding assessment, “Data were recorded by one of the research team members who [was] not involved in anaesthetic management of the case.” Of course, the strategy depends on the study outcome. So, when blinding assessors is not possible, participants could be blinded to the study objectives [32].

Another bias could be introduced by the lack of standardization of the primary outcome. For example, Curtis *et al.* [16] defined peripheral intravenous catheterization as a clear flush through

the catheter with 5 mL normal saline without extravasation. This arbitrary definition could limit the generalization of results and result in heterogeneity in future meta-analyses.

With only 25% of the interventions being fully reported, dissemination of study findings is at risk. Items most limiting reproducibility were “who” performed the intervention and “when and how much” was performed. By reading the methods section of articles, we could not determine the background of participants. In fact, knowing the educational level of the operators is essential to interpreting the results. In some specialties, the certifying college imposes a minimum and standardized level for performing US [33]. For example, in cardiology, all physicians independently interpreting echocardiograms must have a minimum of level II training in transthoracic echography imaging as defined by the American College of Cardiology/American Heart Association/American College of Physicians-American Society of Internal Medicine Task Force on Clinical Competence in Echocardiography, or its equivalent, and must meet annual criteria to maintain that competence [34]. As for other areas in emergency medicine, differing levels of expertise exist in the real world of health care and affect the success of any intervention integrated into bedside care [35-36]. The background of each specialty training must be accessible and published. In France, we are currently working on standardizing training and skills in US [37]. Finally, the intensity of the intervention was poorly reported by authors. In fact, in an emergency situation, the duration and number of interventions performed and the learning curve are of undeniable importance. The aim of US is to save time in the care of patients. All these limits illustrate that ultrasound technology in emergency medicine features a paradox known as “Buxton's Law” [38]: it is always too early to rigorously evaluate a new technology until it is suddenly too late because almost all practitioners have adopted the method because of convenience, preference, or other reasons.

Our study has several limitations. First, we could have omitted some studies because we performed our research in only one database (i.e., MEDLINE via PubMed). However, we performed an exhaustive research and MEDLINE gives an overview of research. Second, for the assessment of the methodological quality, authors might have omitted key information from reports that was deleted during the publication process, and we were able to assess published reports only.

5. CONCLUSION

Despite high clinical interest in US, few RCTs have evaluated an ultrasound intervention in emergency medicine. Moreover, the quality of these trials raises questions. In our sample, authors did not correctly report blinding of participants and outcome assessors or allocation concealment. Authors must ensure that they report all key items of RCTs to allow reproducibility of the intervention and generalizability of results.

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Contributors

Conception and design: AC, QD and YY; Acquisition of data, AC and QD; Analysis: AC; Interpretation of data: AC, QD, PP, DP and YY; Drafting the article: AC, QD, PP, DP and YY; Revising it critically for important intellectual content: AC, QD, PP, DP and YY; Final approval of the version to be published: AC, QD, PP, DP and YY.

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Conflicts of interest

The authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization other than the funding agency listed above for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Appendix 1. Details of included studies and risk of bias ratings

First Author	Objective	Intervention	Comparator	Operators	Primary Outcome	Risk of Bias
Ha [14]	Whether a modified carotid sinus massage (CSM) using US is superior to the conventional CSM for vagal tone generation	Using US for tracking carotid sinus	Usual procedure	Medical students	Mean differences between pre- and post-maneuver and R-R intervals and heart rates	-Se: Low -Al: Unclear -BP: High -BA: Unclear -In: Low -Sr: Unclear
Ahn [15]	Whether the addition of US to traditional physical examination instruction improves junior medical students' abilities to locate the femoral pulse.	Using US for tracking femoral axis	Usual procedure	Medical students	The distance between the student's marker and the invisible ink marking for the femoral artery	-Se: Unclear -Al: Unclear -BP: Low -BA: Low -In: Low -Sr: Unclear
Curtis [16]	The effectiveness of the use of US or near-infrared vascular imaging to guide catheterization	Using US for catheterisation	Usual procedure	Nurses	Successful catheter placement on the first attempt	-Se: Low -Al: Low -BP: Unclear -BA: Low -In: Low -Sr: Unclear
Vogel [17]	Comparing the efficiency and outcomes of the long axis and the short axis views in ultrasound-guided catheterization		Long axis versus short axis	Resident physicians	Time to cannulation, number of skin breaks and redirections, and posterior wall penetration	-Se: Unclear -Al: unclear -BP: Low -BA: High -In: Low -Sr: Unclear
Stewart [18]	The effect of BRIPPED on the physicians' lists of differential diagnoses for patients presenting with shortness of breath	Standardized ultrasound evaluation of pulmonary B-lines, right ventricle, size and strain, inferior vena cava collapsibility, pleural and pericardial effusion, pneumothorax, ejection fraction of the left ventricle (LV), and lower	Usual procedure	Emergency physicians and residents	The magnitude of change in the differential diagnosis after the BRIPPED scan compared with the magnitude of change of the differential diagnosis after routine evaluation with all accompanying laboratory tests and radiographic imaging for undifferentiated shortness	-Se: Low -Al: Low -BP: Low -BA: Low -In: Low -Sr: Low

		extremity deep venous thrombosis			of breath	
Ozkan [19]	The accuracy of point-of-care US (PoCUS) and stethoscopes as part of the physical examinations of patients with dyspnea	Visual examination of patients with dyspnea by PoCUS according to their randomized group	Usual procedure	Medical students	Diagnosis of the dyspnea	-Se: Low -Al: Unclear -BP: Unclear -BA: Unclear -In: Low -Sr: Unclear
Strnad [20]	The usefulness of prehospital lung US in monitoring the effectiveness of treatment with continuous positive airway pressure	Sonographic examination, consisting of 15 intercostal spaces	Usual procedure	Pre-hospital emergency physicians	Respiratory rate, mean arterial pressure; partial pressure of end-tidal carbon dioxide; arterial oxygen saturation, heart rate and total number of B-lines	-Se: Unclear -Al: Unclear -BP: Unclear -BA: Unclear -In: Low -Sr: Unclear
Bentley [21]	Comparing the test, survey, and performance of US between medical students trained on an ultrasound simulator versus those trained via traditional, hands-on patient format	A standardized, introductory lecture on the use of US, FAST basics and indications, and how to conduct a FAST exam	Usual procedure	Emergency medical students	Comparison of ultrasound knowledge between pre- and post-test scores to assess ultrasound knowledge; comparison of pre- and post-survey results of comfort with use of US; and the results of the objective structured clinical examination, specifically the ability of a student to perform critical actions required to successfully identify and interpret normal and pathologic images on FAST	-Se: High -Al: Unclear -BP: Unclear -BA: Unclear -In: Low -Sr: Unclear
Paddock [22]	Comparing the effectiveness of a novel portable ultrasound simulator with traditional FAST skills training for a deployed mixed provider disaster response team	US Simulator Skills Training	Usual procedure	Disaster team	FAST image acquisition and interpretation skills assessment scores	-Se: Unclear -Al: Unclear -BP: Unclear -BA: Unclear -In: Low -Sr: Unclear

Sohoni [23]	The efficacy of hand anesthesia produced by ultrasound-guided forearm nerve blocks	Nerve block with US guidance	Usual procedure	Experts in anaesthesiology	Success of nerve block	-Se: Low -Al: Unclear -BP: low -BA: Unclear -In: Low -Sr: Unclear
Chaudery [24]	Whether contrast-enhanced ultrasonography can improve the accuracy of resuscitative endovascular balloon occlusion of the aorta (REBOA) placement in the infrarenal aorta	Addition of US guidance and a balloon contrast medium	Usual procedure	Emergency physicians and residents	Time (seconds) from insertion to inflation, accuracy, and missed targets	-Se: Low -Al: Low -BP: Unclear -BA: Unclear -In: Low -Sr: Unclear

(US: ultrasonography, Se: sequence generation, Al: allocation concealment, BP: blinding of participants, BA: blinding of assessors, In: incomplete outcome, Sr: selective reporting, FAST: Focused Assessment with Sonography for Trauma)

Appendix 2. Reporting of key items for reproducibility of the intervention.

Items for interventions	n (%)	All items n (%)	“What, Who, Where, When and how much” items n (%)
What (materials): physical or informational materials used, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed	10 (90.9%)	3 (25)	3 (25)
What (procedures): the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	11 (100%)		
Who provided: for each category of intervention provider, describe their expertise, background and any specific training given.	8 (72.7%)		
Where: describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	11 (100%)		
When and how much: describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	4 (36.3%)		
How well (planned): intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	3 (27.3%)		
How well (actual): intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	1 (9.1%)		

Figure 1. The flow of reports of randomized controlled trials of ultrasonography in the study.

Table 1. Characteristics of included studies

Publishing journal	
<i>American Journal of Emergency Medicine</i>	3 (27.3)
<i>European Journal of Emergency Medicine</i>	2 (18.2)
<i>The Western Journal of Emergency Medicine</i>	2 (18.2)
<i>Critical Care Medicine</i>	1 (9.1)
<i>Journal of Ultrasound in Medicine</i>	1 (9.1)
<i>The Journal of Trauma and Acute Care Surgery</i>	1 (9.1)
<i>Canadian Medical Association Journal</i>	1 (9.1)
Country	
Europe	3 (27.3)
North America	7 (63.6)
Asia	1 (9.1)
Time to publication, days, median [IQR]	88 [57-143]
No. of centers involved	
Single-center study	11 (100)
Multi-center study	0 (0)
No. of operators, median [IQR]	36 [16-65]
Ethical committee approval	9 (81.8)
Registration or study protocol available	1 (9.1)

Table 2. Assessment of risk of bias of included studies (n=11)

	Low Risk	Unclear Risk	High Risk
Random sequence generation	6 (54.5)	5 (45.5)	0 (0)
Allocation concealment	3 (27.3)	8 (72.7)	0 (0)
Blinding of participants	3 (27.3)	7 (63.6)	1 (9.1)
Blinding of outcome assessors	3 (27.3)	7 (63.6)	1 (9.1)
Attrition bias (incomplete outcome data)	11 (100)	0 (0)	0 (0)
Selective outcome reporting	1 (9.1)	10 (90.9)	0 (0)

Figure 1