Interventions to reduce arterial puncture-related pain: A systematic review and meta-analysis

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Abstract

Background
Arterial puncture-related pain remains unaddressed across several clinical settings. Analgesic techniques are not routinely employed before arterial puncture despite the recommendation that local anesthesia be used, except in emergencies. A comprehensive review of interventions aimed at reducing arterial puncture-related pain and their potential effectiveness is lacking, and the benefit of some interventions is uncertain.

Objective
To describe interventions aimed at reducing arterial puncture-related pain and provide an estimate of their effectiveness.

Design
Systematic review and meta-analysis (PROSPERO no. CRD42020212299).
Data source(s)
PubMed, CINAHL EBSCO, EMBASE, the Cochrane Database of Systematic Reviews, and Scopus were searched from their inception to 7 October 2020. No temporal or language limits were applied.

Methods
Published, quantitative studies on interventions aimed at reducing arterial puncture-related pain among adults were included. Screening, quality appraisal, and data extraction were undertaken independently by two reviewers. Random effects meta-analyses were performed to assess the association between interventions aimed at reducing arterial puncture-related pain and patients' perceived pain using difference in means (MD) with 95% confidence intervals (CIs). A funnel plot and Egger test were used to assess publication bias.

Results
The titles and abstracts of the 2446 identified articles were screened, and 43 and 31 studies were finally included in the systematic review and meta-analysis, respectively. Interventions to reduce arterial puncture-related pain included: topical anesthetics (*n* = 16), cryotherapy (*n* = 9), local anesthetic infiltration (*n* = 5), narrower needle gage (*n* = 5), ultrasound-guided procedure (*n* = 3), topical anesthetics combined with local anesthetic infiltration (*n* = 1), iontophoresis using anesthetics (*n* = 1), engineered blood gas syringe (*n* = 1), jet injector (*n* = 1), and local massage (*n* = 1). Topical anesthetics [MD -0.58, 95% CI -1.00, -0.15], cryotherapy [MD -1.13, 95% CI -1.72, -0.53], and local anesthetic infiltration [MD -1.13, 95% CI -1.72, -0.53] reduced arterial puncture-related pain. No benefit was found for narrower needle gage [MD -0.07, 95% CI -0.86, 0.71] or ultrasound-guided procedure [MD -1.74, 95% CI -3.51, 0.03]. No publication bias was detected.

Conclusions
Local anesthetic infiltration provided the greatest pain reduction and should be considered standard practice. Cryotherapy may be a safe, convenient alternative to local anesthetic infiltration. Topical anesthetics had limited benefit, and their lengthy time of onset makes them unsuitable for critical or emergency situations, though they may represent an option when comorbid conditions make cooling impossible. Caution must be used when interpreting these results, given the high risk of bias in the methods of included studies and the heterogeneity across the studies.

Keywords: Analgesia; Blood specimen collection; Blood gas analysis; Pain management; Pain; Procedural.

What is already known

- Scientific societies and organizations recommend the control of procedural pain.
- Patients rank arterial puncture among the most painful procedures.
- Analgesic techniques are not routinely employed before arterial puncture despite the recommendation that local anesthesia be used, except in emergencies.
- A comprehensive review of interventions aimed at reducing arterial puncture-related pain and their potential effectiveness is lacking, and the benefit of some interventions is uncertain.

What this paper adds

- Local anesthetic infiltration provides the greatest pain reduction after arterial puncture and should be considered standard practice.
- Cryotherapy may be a valid alternative to local anesthetic infiltration due to its safe, easy-to-apply, non-invasive profile, in addition to its rapid effect and favorable cost-benefit ratio.
- Topical anesthetics have limited benefit, and their lengthy time of onset may not be suitable for critical or emergency situations, though they may be an option when cooling is not possible.

1. Introduction

Arterial puncture is performed to collect blood samples for arterial blood gas analysis or to establish an arterial access, and is a common procedure in a variety of clinical settings (Hudson et al., 2006). Each year, arterial blood gas analysis alone accounts for 1,000 arterial punctures in average-sized hospitals and over 10,000 in large hospitals (Melanson et al., 2007; 2014). In emergency settings, 8% to 12% of patients receive arterial puncture for blood gas analysis purposes (Bobbia et al., 2013), while around 36% of patients treated in Intensive Care have an arterial access in place (Gershengorn et al., 2014). Patients are usually awake during arterial puncture, which puts them at increased risk of procedural pain (Angelini et al., 2011) and anxiety (Patout et al., 2015; Lasocki et al., 2020). Medical patients ranked arterial puncture as the third most painful experience after bone marrow biopsy and colonoscopy, and higher than esophagus-gastro-duodenoscopy, thoracentesis, and bronchoscopy (Angelini et al., 2011). Patients in intensive care units reported that arterial puncture caused greater anxiety than tracheal aspiration (Turner et al., 1990). Among patients who ranked arterial puncture among the most painful procedures, over 70% would have desired local anesthetics or anxiolytics before the procedure, but no drug was ever administered (Angelini et al., 2011).

Pain management is a globally recognized indicator of quality of care (Brennan et al., 2016), and scientific societies and organizations underline the importance of controlling procedural pain (Cooney et al., 2013; Czarnecki et al., 2011). However, analgesic techniques are not routinely employed before arterial puncture (Valero Marco et al., 2008; Zinchenko et al., 2016), despite the recommended use of local anesthesia, except in emergencies (O'Driscoll et al., 2017; World Health Organization, 2010). A survey of 153 healthcare professionals across different clinical settings reported that over half of them never used local anesthetic infiltration before arterial puncture, and about one-third used it “sometimes”, despite the fact that over 80% judged arterial puncture to be quite to extremely painful (Zinchenko et al., 2016). Similarly, a study exploring use of local anesthesia among 131 Spanish nurses found that only 5% employed local anesthetic infiltration

routinely (Valero Marco et al., 2008). Common reasons for not using local anesthetic infiltration included lack of training (Valero Marco et al., 2008; Zinchenko et al., 2016; Lightowler and Elliott, 1997), and the false belief that local anesthetic infiltration is as painful as arterial puncture, offers no benefit in terms of pain reduction, lengthens and increases the difficulty of the procedure, reduces the success rate, and that pain from arterial puncture is no more than that from venipuncture (Hudson et al., 2006). In their telephone survey, Lightowler and Elliot found that almost half of the 101 physicians surveyed thought that injecting a local anesthetic would be just as painful as the arterial puncture itself. However, physicians then rated the procedure as less painful when local anesthetic infiltration was used, and they did not report increased difficulty with infiltration (Lightowler and Elliott, 1997). Moreover, patients reported arterial puncture to be more painful than venipuncture (Giner et al., 1996), likely due to the fact that the arterial wall has many more pain receptors than the venous wall, and that the skin needs to be punctured deeper to reach an artery (Hudson et al., 2006).

Several alternatives to local anesthetic infiltration have been proposed to reduce arterial puncture-related pain; topical anesthetics (Aguilar et al., 2007; Cortés-Télles et al., 2012, García García et al., 2005, Giner et al., 2000, Joly et al., 1998, Kim et al., 2007, Latsios et al., 2017, Mayoral et al., 2010, Olday et al., 2002, Russell et al., 1988, Guevara Sanz and Conde Anguita, 2001, Smith et al., 1990, Tran et al., 2002, Aaron et al., 2003, Micu et al., 2006, Ruetzler et al., 2012), rapid cooling of the puncture site (Ballesteros-Peña et al., 2017, Bastami et al., 2015, Farahmand et al., 2017, Haynes, 2015, Khalil, 2017, L'Her et al., 2001, Mahto et al., 2016, Pagnucci et al., 2020, Rüsch et al., 2017), and the use of narrower needle gauges (Patout et al., 2015, Giner et al., 1997, Ibrahim et al., 2015, Guevara Sanz and Requena Castillo, 2011, Yee et al., 2015) are the most frequently investigated. These alternatives may be useful to overcome time constraints, when patients have known reactions to local anesthetic infiltration, or when healthcare professionals want to avoid puncturing patients twice. However, the literature showed no difference in the success rate (Giner et al., 1996, Aaron et al., 2003), puncture attempts (Lightowler and Elliott, 1997, Aaron et al., 2003, France et al., 2008), or time needed to complete the procedure successfully (Latsios et al., 2017, Aaron et al., 2003, Ballesteros-Peña et al., 2017, France et al., 2008) when local anesthesia was employed. Instead, local anesthesia has been found to reduce puncture attempts (Farahmand et al., 2017) and time needed to complete the procedure (Joly et al., 1998, Grandpierre et al., 2019). Similarly, procedural difficulty experienced by healthcare professionals was not influenced by local anesthesia, i.e., topical anesthetics (Aaron et al., 2003, Ruetzler et al., 2012, Hajiseyedjavady et al., 2012), cryotherapy (Ballesteros-Peña et al., 2017), or local anesthetic infiltration (Lightowler and Elliott, 1997). Also, research about ultrasound-guided arterial puncture is developing (Bobbia et al., 2013, Grandpierre et al., 2019, Carpizo et al., 2014); however, evidence is still limited and contrasting, with some authors reporting better success rate at the first puncture (Grandpierre et al., 2019, Carpizo et al., 2014), lower time to complete the procedure successfully (Grandpierre et al., 2019, Carpizo et al., 2014), and higher healthcare professionals' satisfaction when ultrasound guidance was employed (Grandpierre et al., 2019); while others showed no impact on patients' and healthcare professionals' satisfaction and an even increased number of attempts and time of successfully complete procedure (Bobbia et al., 2013).

To our knowledge, there is no comprehensive review of interventions to reduce arterial puncture-related pain. Moreover, results of the effectiveness of such procedures have been mixed, and the benefits of topical anesthetics (Aguilar et al., 2007, Giner et al., 2000, Mayoral et al., 2010, Micu et al., 2006, Pagnucci et al., 2020) and narrower needle gauges (Patout et al., 2015, Giner et al., 1997, Yee et al., 2015) are particularly uncertain.

1.1. Objectives

The aim of this systematic review and meta-analysis is to describe interventions to reduce arterial puncture-related pain and provide an estimate of their effectiveness. To this end, the analysis will provide evidence that will answer the following research questions:

1)Which interventions reduce arterial puncture-related pain?
2)What is the effectiveness of each intervention?

2. Methods

2.1. Design

We conducted a systematic literature review and a meta-analysis according to the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) (Table A1, Appendix 1). The review protocol was registered in the PROSPERO register of systematic reviews on 7 October 2020 (registration number CRD42020212299), available at https://www.crd.york.ac.uk/prospero/display_record.php?ID= CRD42020212299. We made no major amendments to the original protocol.

2.2. Search strategy

To create an exhaustive search strategy and identify the most appropriate keywords, an explorative search of MEDLINE (via PubMed) and CINAHL EBSCO was conducted in September 2020, followed by an analysis of the resultant titles and abstracts. Then, five databases (MEDLINE (via PubMed), CINAHL EBSCO, EMBASE, the Cochrane Database of Systematic Reviews, and Scopus) were searched from their inception to 7 October 2020. One investigator (SG) with extensive experience in searching literature carried out searches with the supervision of a health librarian. Searches employed both thesaurus and free terms, without temporal or language limits. Search strategies were adapted for each database (Appendix 2). Finally, the references of included articles were screened manually to identify further relevant publications. Also, PROSPERO register of systematic reviews was searched for ongoing or recently completed reviews.

2.3. Eligibility criteria

We included interventional studies (i.e., pre-post studies, clinical trials, controlled clinical trials, and randomized controlled trials) published in peer-reviewed journals, regardless of underlying disease and setting (i.e., home, public hospital, private hospital, nursing home, and hospice). To be included in the systematic review, studies had to be conducted on adults (≥18 years) and be focused on interventions aimed at reducing pain associated with arterial puncture (i.e., blood collection for arterial blood gas analysis and arterial catheterization) at whatever puncture site (i.e., radial, brachial, and femoral) in routine practice or in emergencies. Studies focused on interventions aimed at managing pain associated with other procedures (e.g., venipuncture, venous catheterization, and arteriovenous fistula puncture) and studies reporting patients' lived experience of arterial puncture were excluded. Proceedings and research protocols were also excluded.

Meta-analyses were based on studies identified in the systematic review. A separate meta-analysis was conducted for each analgesic intervention as long as it was the object of at least three included studies. If there were fewer than three included studies on the intervention, no meta-analysis was performed.

2.4. Article screening and study selection

Two investigators (AC and SG) independently screened the title and abstract of identified articles, removed duplicates, and reviewed the full texts of the potentially relevant articles. Any disagreement or uncertainty regarding eligibility was addressed through consensus with a third investigator (MC).

2.5. Assessment of risk of bias

Risk of bias was independently assessed by AC and SG using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019). Any disagreement was solved through discussion with a third investigator (MC). The RoB 2 is structured into five domains through which bias might be introduced: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result. Each domain includes signaling questions with five response options (yes, probably yes, probably no, no, and no information). Using algorithms that map responses to these signaling questions, a risk-of-bias judgement (i.e., low risk, some concerns, and high risk) was assigned for each domain. Domain judgements were then combined into an overall risk-of-bias judgement: low (i.e., low risk of bias for all domains), some concerns (i.e., some concerns in one domain and no high risk for any domain), or high (i.e., high risk of bias in at least one domain or some concerns for multiple domains) (Sterne et al., 2019). The Risk-of-bias VISualization was adopted for visualizing risk-of-bias assessments (McGuinness and Higgins, 2021). This web app creates "traffic light" plots of the domain-level judgements for each individual result, and summary bar plots of the distribution of risk-of-bias judgements within each domain.

2.6. Data extraction

Data on study characteristics (author, country, year, study aim, design, type of setting, size of study sample, description of the intervention, outcome(s) investigated, and assessment tools); sample characteristics (number, sex, age, previous arterial puncture, puncture site, reason for arterial puncture [catheterization vs blood collection for arterial blood gas analysis], needle gage for arterial puncture, Allen test [yes vs no], and healthcare professionals performing the procedure); narrative summary of findings; and quantitative results (mean/median pain with standard deviation (SD)/range) were independently extracted by AC and SG, and entered into a data collection form (excel spreadsheet). Disagreements and uncertainties were resolved by consensus with a third researcher (SC). The data collection form was piloted on five studies and appropriate adjustments were made.

2.7. Primary and secondary outcomes

Our primary outcome was patients' perception of arterial puncture-related pain, which was defined as pain during or immediately after the procedure, or overall arterial puncture-related pain experience. When the time of assessment was not clearly specified, we categorized it as pain during the procedure. When pain was assessed at several time points, we only extracted information on pain during the procedure. The primary outcome was expressed as the mean on a Numeric Rating Scale (NRS) 0–10 with SD. Conversion was applied if necessary (e.g., when pain was expressed as mean on NRS 0–100 or median).

All other arterial puncture-related outcomes reported across studies were labelled as secondary outcomes.

2.8. Data synthesis

Difference in means (MD) on NRS 0–10 in arterial puncture-related pain was the measure chosen for the primary outcome, calculated by subtracting the mean values in two different groups. We adopted a random-effects model with unrestricted maximum likelihood, with Hartung-Knapp-Sidik-Jonkman adjustment, using the sample size as a weighting factor (IntHout et al., 2014). Heterogeneity was assessed using the Cochran Q test via a Mantel-Haenszel test based on the pooled MD and was suggested if Q was higher than the degrees of freedom. Then, it was confirmed by $p \leq 0.10$ and by means of the I^2 statistic as proposed by Higgins and Thompson: I^2 values of 0 to 24.9%, 25% to 49.9%, 50% to 74.9%, and >75% were considered as none, low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). The funnel plot was visually inspected, and the Egger's test was performed to assess publication bias (Egger et al., 1997). As a further investigation,

we carried out subgroup analyses based on the reason for arterial puncture to assess the association between different interventions aimed at relieving arterial puncture-related pain and patients' perception of arterial puncture-related pain, using MDs with 95% confidence intervals (CIs). A mixed-effect model was employed, and a Q test was performed to assess significant differences among groups. Results were considered statistically significant at two-tail $p<0.05$. All analyses were carried out in R version 4.0.2 statistical software.

3. Results

3.1. Articles included in systematic review and meta-analysis

The search strategy rendered 2446 articles. The screening of titles and abstracts led to the identification and removal of 932 duplicates and the inclusion of 46 articles into the full text review process. Twelve (Bates and Cutting, 2001, Wendler, 2003, Çelik et al., 2011, Chauvin et al., 2020, Chvetzoff, 2006, Dawson and Hogg, 2005, Eslami et al., 2020, Li et al., 2016, McSwain and Yeager, 2015, Ouadhour et al., 2008, Pouso Garrido, 2017, Stewart et al., 2021) did not meet the inclusion criteria and were excluded (Table A2, Appendix 1). The manual review of included papers revealed nine additional articles, thus 43 articles were included in the systematic review (Fig. 1). Five of the 43 articles included in the systematic review were not eligible for inclusion in the meta-analysis, as they covered analgesic interventions that were the object of fewer than three studies. Additional data were requested from the authors of the 38 remaining studies for data conversion, but the authors of seven articles did not answer (García García et al., 2005, Joly et al., 1998, Mayoral et al., 2010, Russell et al., 1988, Guevara Sanz and Conde Anguita, 2001, Smith et al., 1990, Guevara Sanz and Requena Castillo, 2011). Therefore, we had to exclude these seven articles for the following reasons: because mean pain values were lacking (García García et al., 2005, Mayoral et al., 2010, Guevara Sanz and Conde Anguita, 2001, Smith et al., 1990, Guevara Sanz and Requena Castillo, 2011) or pain values could not be converted to the measure chosen for the primary outcome (i.e., mean on NRS 0-100), because median pain values were reported without interquartile range (Russell et al., 1988), or because pain was expressed as median with 10th-90th percentile (Joly et al., 1998). Therefore, 31 articles were finally included in the meta-analytic process.

3.2. Characteristics of studies included in the systematic review

The included studies were conducted in 17 countries: 10 in Spain (Giner et al., 1996, Aguilar et al., 2007, García García et al., 2005, Giner et al., 2000, Mayoral et al., 2010, Guevara Sanz and Conde Anguita, 2001, Ballesteros-Peña et al., 2017, Giner et al., 1997, Guevara Sanz and Requena Castillo, 2011, Carpizo et al., 2014), seven in France (Bobbia et al., 2013, Patout et al., 2015, Lasocki et al., 2020, Joly et al., 1998, Micu et al., 2006, L'Her et al., 2001, Grandpierre et al., 2019), seven in the United Kingdom (Lightowler and Elliott, 1997, Olday et al., 2002, Russell et al., 1988, Smith et al., 1990, France et al., 2008, Sherwin et al., 2003, Wade et al., 2015), three in Iran (Bastami et al., 2015, Farahmand et al., 2017, Hajiseyedjavady et al., 2012), two in Turkey (Baskın et al., 2014, Tatlı et al., 2018), two in the United States (Matheson et al., 2014, Haynes, 2015), two in Australia (Tran et al., 2002, Yee et al., 2015), one in Canada (Aaron et al., 2003), one in Mexico (Cortés-Télles et al., 2012), one in Singapore (Ibrahim et al., 2015), one in Egypt (Khalil, 2017), one in South Korea, (Kim et al., 2007) one in Greece (Latsios et al., 2017), one in India (Mahto et al., 2016), one in Italy (Pagnucci et al., 2020), one in Austria (Ruetzler et al., 2012), and one in Germany (Rüsch et al., 2017) (Table 1). Five of the studies were published before 2000 (Lightowler and Elliott, 1997, Giner et al., 1996, Russell et al., 1988, Smith et al., 1990, Giner et al., 1997), 16 between 2000 and 2010 (Matheson et al., 2014, Aguilar et al., 2007, García García et al., 2005, Giner et al., 2000, Joly et al., 1998, Kim et al., 2007, Mayoral et al., 2010, Olday et al., 2002, Guevara Sanz and Conde Anguita, 2001, Tran et al., 2002, Aaron et al., 2003, Micu et al., 2006, L'Her et al., 2001, France et al., 2008, Grandpierre et al., 2019, Sherwin et al., 2003), and 22 after 2010 (Bobbia et al., 2013, Patout et al., 2015, Lasocki et al., 2020, Cortés-Télles et al.,

2012, Latsios et al., 2017, Ruetzler et al., 2012, Ballesteros-Peña et al., 2017, Bastami et al., 2015, Farahmand et al., 2017, Haynes, 2015, Khalil, 2017, Mahto et al., 2016, Pagnucci et al., 2020, Rüsch et al., 2017, Ibrahim et al., 2015, Guevara Sanz and Requena Castillo, 2011, Yee et al., 2015, Hajiseyedjavady et al., 2012, Carpizo et al., 2014, Wade et al., 2015, Baskın et al., 2014, Tatlı et al., 2018). All studies were parallel trials except two (Lasocki et al., 2020, Ibrahim et al., 2015) which had a crossover design. Twenty-two (Bobbia et al., 2013, Lasocki et al., 2020, García García et al., 2005, Joly et al., 1998, Latsios et al., 2017, Olday et al., 2002, Russell et al., 1988, Bastami et al., 2015, Haynes, 2015, Khalil, 2017, L'Her et al., 2001, Mahto et al., 2016, Pagnucci et al., 2020, Giner et al., 1997, Guevara Sanz and Requena Castillo, 2011, France et al., 2008, Grandpierre et al., 2019, Hajiseyedjavady et al., 2012, Carpizo et al., 2014, Wade et al., 2015, Baskın et al., 2014, Tatlı et al., 2018) studies were open, 13 (Aaron et al., 2003, Aguilar et al., 2007, Farahmand et al., 2017, Giner et al., 1996, Giner et al., 2000, Guevara Sanz and Conde Anguita, 2001, Kim et al., 2007, Lightowler and Elliott, 1997, Mayoral et al., 2010, Patout et al., 2015, Ruetzler et al., 2012, Smith et al., 1990, Tran et al., 2002) were double-blinded, and eight (Matheson et al., 2014, Cortés-Télles et al., 2012, Micu et al., 2006, Ballesteros-Peña et al., 2017, Rüsch et al., 2017, Ibrahim et al., 2015, Yee et al., 2015, Sherwin et al., 2003) were single-blinded. Sixteen (Matheson et al., 2014, Lightowler and Elliott, 1997, Giner et al., 1996, Giner et al., 2000, Kim et al., 2007, Mayoral et al., 2010, Guevara Sanz and Conde Anguita, 2001, Smith et al., 1990, Tran et al., 2002, Ruetzler et al., 2012, Rüsch et al., 2017) studies were placebo-controlled.

Fourteen (Bobbia et al., 2013, Ballesteros-Peña et al., 2017, Farahmand et al., 2017, Khalil, 2017, L'Her et al., 2001, Pagnucci et al., 2020, Ibrahim et al., 2015, Yee et al., 2015, France et al., 2008, Grandpierre et al., 2019, Hajiseyedjavady et al., 2012, Carpizo et al., 2014, Wade et al., 2015, Baskın et al., 2014) studies were performed in emergency units, five (Matheson et al., 2014, Lasocki et al., 2020, Russell et al., 1988, Mahto et al., 2016, Rüsch et al., 2017) in anesthesiology or intensive care units, and two (Matheson et al., 2014, Sherwin et al., 2003) in medical or surgical units. Six (Lightowler and Elliott, 1997, Mayoral et al., 2010, Smith et al., 1990, Bastami et al., 2015, Giner et al., 1997, Guevara Sanz and Requena Castillo, 2011) studies generally referred to the hospital setting, while four (Aguilar et al., 2007, Giner et al., 2000, Guevara Sanz and Conde Anguita, 2001) did not provide any information on study setting. Seven (Patout et al., 2015, Giner et al., 1996, Cortés-Télles et al., 2012, Tran et al., 2002, Aaron et al., 2003, Micu et al., 2006, Haynes, 2015) studies specifically involved patients with pulmonary diseases, and six (Joly et al., 1998, Kim et al., 2007, Latsios et al., 2017, Olday et al., 2002, Ruetzler et al., 2012, Tatlı et al., 2018) included patients with cardiovascular diseases. Sample size was extremely variable across studies, ranging from less than 50 (Aguilar et al., 2007, Hajiseyedjavady et al., 2012, L'Her et al., 2001, Matheson et al., 2014, Sherwin et al., 2003, Wade et al., 2015) to over 500 (Baskın et al., 2014, Joly et al., 1998, Pagnucci et al., 2020) patients, with a median size of 90 patients. Study samples comprised fewer females than males, who represented about 60% of all patients involved. Three (Lasocki et al., 2020, Joly et al., 1998, Sherwin et al., 2003) studies enrolled more than 80% male patients, while females were more represented in six of the 43 studies (Bobbia et al., 2013, Cortés-Télles et al., 2012, Haynes, 2015, Rüsch et al., 2017, Ibrahim et al., 2015, Grandpierre et al., 2019). Mean age was 61 years and ranged from 32 (Ibrahim et al., 2015) to 73 (Carpizo et al., 2014, Grandpierre et al., 2019, Guevara Sanz and Conde Anguita, 2001) years. In five studies (Patout et al., 2015, Tran et al., 2002, Aaron et al., 2003, Bastami et al., 2015, Haynes, 2015), patients had already had previous arterial puncture experience (ranged from 20% (Aaron et al., 2003) to all (Guevara Sanz and Conde Anguita, 2001, Guevara Sanz and Requena Castillo, 2011) patients).

Four studies were classified as having a low risk of bias, three provided some concerns, and 36 were classified as having a high risk of bias. Bias due to deviations from intended interventions, bias in the selection of the reported result, and bias arising from the randomization process were those of greatest concern. The risk of bias is presented for each study in Figure A1, Appendix 1, and as a

summary of the distribution of risk-of-bias judgements within each bias domain in Figure A2, Appendix 1. A funnel plot of MDs by the size of the study sample is shown in Figure A3, Appendix 1. No publication bias was detected (Egger test $p = 0.11$).

3.3. Arterial puncture procedure

Arterial puncture was always an elective procedure performed at the radial site except in two (Lightowler and Elliott, 1997, García García et al., 2005) studies, which did not specify the access site. Arterial puncture was performed by physicians ($n = 20$) (Bobbia et al., 2013, Lightowler and Elliott, 1997, Giner et al., 1996, Joly et al., 1998, Kim et al., 2007, Latsios et al., 2017, Olday et al., 2002, Russell et al., 1988, Tran et al., 2002, Farahmand et al., 2017, Haynes, 2015, Rüsch et al., 2017, Ibrahim et al., 2015, Yee et al., 2015, France et al., 2008, Grandpierre et al., 2019, Hajiseyedjavady et al., 2012, Wade et al., 2015, Baskın et al., 2014, Tatlı et al., 2018), nurses ($n = 11$) (Matheson et al., 2014, Patout et al., 2015, Lasocki et al., 2020, Mayoral et al., 2010, Guevara Sanz and Conde Anguita, 2001, Micu et al., 2006, Ballesteros-Peña et al., 2017, L'Her et al., 2001, Pagnucci et al., 2020, Guevara Sanz and Requena Castillo, 2011, Carpizo et al., 2014), respiratory therapists ($n = 4$) (Cortés-Télles et al., 2012, Tran et al., 2002, Aaron et al., 2003, Mahto et al., 2016), and experienced researchers ($n = 2$) (Bastami et al., 2015, Khalil, 2017). Six (García García et al., 2005, Giner et al., 2000, Smith et al., 1990, Ruetzler et al., 2012, Giner et al., 1997, Sherwin et al., 2003) studies did not report who performed the procedure (Table 1). Ten (Joly et al., 1998, Kim et al., 2007, Latsios et al., 2017, Olday et al., 2002, Russell et al., 1988, Smith et al., 1990, Ruetzler et al., 2012, Rüsch et al., 2017, Sherwin et al., 2003, Tatlı et al., 2018) studies explored pain due to arterial catheterization; the others investigated pain due to blood collection for arterial blood gas analysis. When arterial catheterization was performed, a needle gage of 17.5 (Russell et al., 1988), 18 (Joly et al., 1998), or 20 (Kim et al., 2007, Latsios et al., 2017, Olday et al., 2002, Ruetzler et al., 2012, Rüsch et al., 2017, Sherwin et al., 2003, Smith et al., 1990, Tatlı et al., 2018) was employed. Blood collection for arterial blood gas analysis was performed using a needle gage of 22 (Giner et al., 1996, Ballesteros-Peña et al., 2017, Pagnucci et al., 2020, Giner et al., 1997, Guevara Sanz and Requena Castillo, 2011), 23 (Patout et al., 2015, Mayoral et al., 2010, Aaron et al., 2003, Farahmand et al., 2017, Haynes, 2015, Mahto et al., 2016, Ibrahim et al., 2015, Yee et al., 2015, France et al., 2008, Grandpierre et al., 2019), 25 (Patout et al., 2015, Tran et al., 2002, Bastami et al., 2015, Khalil, 2017, Giner et al., 1997, Guevara Sanz and Requena Castillo, 2011, Yee et al., 2015, Wade et al., 2015, Baskın et al., 2014) 26, (Micu et al., 2006, Mahto et al., 2016, Baskın et al., 2014), 27 (Cortés-Télles et al., 2012), and 29 (Hajiseyedjavady et al., 2012, Ibrahim et al., 2015, Lightowler and Elliott, 1997). An Allen test was performed in 15 studies (Matheson et al., 2014, Bobbia et al., 2013, Patout et al., 2015, Cortés-Télles et al., 2012, Kim et al., 2007, Olday et al., 2002, Tran et al., 2002, Aaron et al., 2003, Ruetzler et al., 2012, Ballesteros-Peña et al., 2017, Farahmand et al., 2017, Pagnucci et al., 2020, Carpizo et al., 2014, Wade et al., 2015, Baskın et al., 2014) (in three cases before arterial catheterization).

3.4. Assessment of arterial puncture-related pain

Twenty-one (Bobbia et al., 2013, Patout et al., 2015, Lightowler and Elliott, 1997, Joly et al., 1998, Kim et al., 2007, Latsios et al., 2017, Russell et al., 1988, Guevara Sanz and Conde Anguita, 2001, Smith et al., 1990, Tran et al., 2002, Pagnucci et al., 2020, Giner et al., 1997, Ibrahim et al., 2015, Yee et al., 2015, France et al., 2008, Grandpierre et al., 2019, Carpizo et al., 2014, Sherwin et al., 2003, Wade et al., 2015, Baskın et al., 2014, Tatlı et al., 2018) studies in the systematic review explored patients' perception of arterial puncture-related pain during the procedure, 12 (Aaron et al., 2003, Aguilar et al., 2007, Ballesteros-Peña et al., 2017, Bastami et al., 2015, Cortés-Télles et al., 2012, Farahmand et al., 2017, Giner et al., 1996, Hajiseyedjavady et al., 2012, Haynes, 2015, Khalil, 2017, L'Her et al., 2001, Olday et al., 2002) immediately after the procedure, and one (Rüsch et al., 2017) explored overall pain experience.

Seven studies (Matheson et al., 2014, García García et al., 2005, Giner et al., 2000, Mayoral et al., 2010, Micu et al., 2006, Mahto et al., 2016, Guevara Sanz and Requena Castillo, 2011) did not specify the timing of pain assessment and instead generally referred to arterial puncture-related pain. Finally, three (Matheson et al., 2014, Lasocki et al., 2020, Ruetzler et al., 2012) studies assessed pain at several time points.

Different tools were used to assess arterial puncture-related pain, including the Visual Analogue Scale (VAS) 0–10 (*n* = 20) (Matheson et al., 2014, Giner et al., 1996, Aguilar et al., 2007, Giner et al., 2000, Latsios et al., 2017, Mayoral et al., 2010, Olday et al., 2002, Smith et al., 1990, Micu et al., 2006, Ballesteros-Peña et al., 2017, Bastami et al., 2015, Khalil, 2017, Mahto et al., 2016, Giner et al., 1997, Yee et al., 2015, Hajiseyedjavady et al., 2012, Sherwin et al., 2003, Wade et al., 2015, Baskın et al., 2014, Tatlı et al., 2018), the VAS 0–100 (*n* = 11) (Patout et al., 2015, Cortés-Télles et al., 2012, Kim et al., 2007, Russell et al., 1988, Tran et al., 2002, Aaron et al., 2003, Ruetzler et al., 2012, Haynes, 2015, L'Her et al., 2001, Ibrahim et al., 2015, France et al., 2008), a NRS 0–10 (*n* = 6) (Bobbia et al., 2013, Lasocki et al., 2020, Farahmand et al., 2017, Pagnucci et al., 2020, Rüsch et al., 2017, Carpizo et al., 2014), a 4-point Likert scale (*n* = 3) (Lightowler and Elliott, 1997, Guevara Sanz and Conde Anguita, 2001, Guevara Sanz and Requena Castillo, 2011), and a Verbal NRS (*n* = 2) (Joly et al., 1998, Grandpierre et al., 2019). One (García García et al., 2005) study did not specify the tool used (Table 1).

3.5. Interventions to reduce arterial puncture-related pain

Included studies assessed different strategies to reduce arterial puncture-related pain, including topical anesthetics (*n* = 16) (Aguilar et al., 2007, Cortés-Télles et al., 2012, García García et al., 2005, Giner et al., 2000, Joly et al., 1998, Kim et al., 2007, Latsios et al., 2017, Mayoral et al., 2010, Olday et al., 2002, Russell et al., 1988, Guevara Sanz and Conde Anguita, 2001, Smith et al., 1990, Tran et al., 2002, Aaron et al., 2003, Micu et al., 2006, Ruetzler et al., 2012), cryotherapy (*n* = 9) (Ballesteros-Peña et al., 2017, Bastami et al., 2015, Farahmand et al., 2017, Haynes, 2015, Khalil, 2017, L'Her et al., 2001, Mahto et al., 2016, Pagnucci et al., 2020, Rüsch et al., 2017), local anesthetic infiltration (*n* = 5) (Matheson et al., 2014, Lightowler and Elliott, 1997, Giner et al., 1996, France et al., 2008, Wade et al., 2015), narrower needle gage (*n* = 5) (Patout et al., 2015, Giner et al., 1997, Ibrahim et al., 2015, Guevara Sanz and Requena Castillo, 2011, Yee et al., 2015), ultrasound-guided procedure (*n* = 3) (Bobbia et al., 2013, Grandpierre et al., 2019, Carpizo et al., 2014), topical anesthetics combined with local anesthetic infiltration (*n* = 1) (Tatlı et al., 2018), iontophoresis using anesthetics (*n* = 1) (Sherwin et al., 2003), engineered blood gas syringe (*n* = 1), (Baskın et al., 2014) jet injector (*n* = 1) (Hajiseyedjavady et al., 2012), and local massage (*n* = 1) (Lasocki et al., 2020). A significant difference between interventions was identified ($p<0.01$) (Fig. 2).

3.5.1. Topical anesthetics

Sixteen studies in the systematic review assessed topical anesthetics in the form of gel, cream, ointment, or patch: 10 (Aguilar et al., 2007, García García et al., 2005, Giner et al., 2000, Guevara Sanz and Conde Anguita, 2001, Joly et al., 1998, Kim et al., 2007, Latsios et al., 2017, Mayoral et al., 2010, Russell et al., 1988, Smith et al., 1990) assessed the effect of an eutectic mixture of local anesthetic (EMLA™) cream consisting of 2.5% lidocaine and 2.5% prilocaine; two (Micu et al., 2006, Ruetzler et al., 2012) looked at the EMLA™ patch; two (Olday et al., 2002, Tran et al., 2002) used amethocaine gel; one (Aaron et al., 2003) used tetracaine gel; and one (Cortés-Télles et al., 2012) used lidocaine ointment. A mean dosage of 2.5 g (range 1 g (Giner et al., 2000, Mayoral et al., 2010) to 5 g (Smith et al., 1990)) of EMLA™ cream was applied 30 (García García et al., 2005, Latsios et al., 2017, Mayoral et al., 2010) to 240 (Kim et al., 2007) min before arterial puncture. EMLA™ cream was compared to placebo (*n* = 5) (Aguilar et al., 2007, Giner et al., 2000, Kim et al., 2007, Mayoral et al., 2010, Guevara Sanz and Conde Anguita, 2001), local anesthetic infiltration (*n* = 5) (Giner et al., 2000, Joly et al., 1998, Latsios et al., 2017, Russell et al., 1988, Smith et al., 1990),

or no intervention (*n* = 1) (García García et al., 2005). Two studies tested different timing of EMLA™ application before arterial puncture (30 (García García et al., 2005) and 90min (Russell et al., 1988) vs 60 min). EMLA™ patch was compared to local anesthetic infiltration (Ruetzler et al., 2012), placebo cream (Micu et al., 2006), and no intervention (Micu et al., 2006). Tetracaine gel 4% (Aaron et al., 2003) and lidocaine ointment 5% (Cortés-Télles et al., 2012) were compared to placebo. Amethocaine gel 4% was compared to placebo (Tran et al., 2002) and lidocaine infiltration (Olday et al., 2002).
Ten (Aguilar et al., 2007, Cortés-Télles et al., 2012, Giner et al., 2000, Kim et al., 2007, Latsios et al., 2017, Olday et al., 2002, Tran et al., 2002, Aaron et al., 2003, Micu et al., 2006, Ruetzler et al., 2012) of these studies had data available for the meta-analysis, which showed that topical anesthetics reduced arterial puncture-related pain [MD -0.58, 95% CI -1.00, -0.15] (Fig. 2). The risk of bias in these 10 studies is shown in Figure A4a, Appendix 1.

3.5.2. Cryotherapy
Nine studies assessed cryotherapy, which was performed by local application of ice (Bastami et al., 2015, Haynes, 2015, Khalil, 2017, L'Her et al., 2001, Mahto et al., 2016, Pagnucci et al., 2020) for a median of 3 min (range 30 s (L'Her et al., 2001) to 10 min (Khalil, 2017)) before arterial puncture or by refrigerant spray (Ballesteros-Peña et al., 2017, Farahmand et al., 2017, Rüsch et al., 2017) immediately before arterial puncture. Cryotherapy in the form of crushed ice was compared to no intervention (Bastami et al., 2015, Haynes, 2015, Khalil, 2017, L'Her et al., 2001, Mahto et al., 2016, Pagnucci et al., 2020), EMLA™ cream applied 60 min before arterial puncture (Pagnucci et al., 2020), and mepivacaine infiltration (Pagnucci et al., 2020). Refrigerant spray was compared to placebo spray (Ballesteros-Peña et al., 2017, Khalil, 2017) or 2% lidocaine infiltration (0.5 ml) (Rüsch et al., 2017).
All nine studies had data available for the meta-analysis, which showed that cryotherapy reduced arterial puncture-related pain [MD -1.13, 95% CI -1.72, -0.53] (Fig. 2). The risk of bias among these studies is shown in Figure A4b, Appendix 1.

3.5.3. Local anesthetic infiltration
Four (Matheson et al., 2014, Lightowler and Elliott, 1997, France et al., 2008, Wade et al., 2015) studies assessed lidocaine infiltration, and one (Giner et al., 1996) looked at mepivacaine infiltration. The dosage of theses anesthetics ranged from 0.2 ml[18] to 1 ml (Wade et al., 2015). Local anesthetic infiltration was compared to no intervention (Matheson et al., 2014, Lightowler and Elliott, 1997, Giner et al., 1996, France et al., 2008, Wade et al., 2015), placebo infiltration (Matheson et al., 2014, Lightowler and Elliott, 1997, Giner et al., 1996), buffered anesthetics infiltration (Matheson et al., 2014), and refrigerant anesthetic spray (France et al., 2008).
All five studies had data for the meta-analysis, which showed that local anesthetic infiltration reduced arterial puncture-related pain [MD -1.42, 95% CI -1.86, -0.99] (Fig. 2). The risk of bias among these studies is shown in Figure A4c, Appendix 1.

3.5.4. Narrower needle gage
Five studies in the systematic review tested narrower needle gage compared to large needle alone (Patout et al., 2015, Ibrahim et al., 2015, Guevara Sanz and Requena Castillo, 2011, Yee et al., 2015) or in association with mepivacaine infiltration (Giner et al., 1997). A needle gage of 25 was compared to needle gauges of 22 (Giner et al., 1997, Guevara Sanz and Requena Castillo, 2011) and 23; (Patout et al., 2015, Yee et al., 2015) one study (Ibrahim et al., 2015) compared a needle gage of 29 to a gage of 23.
Four (Patout et al., 2015, Giner et al., 1997, Ibrahim et al., 2015, Yee et al., 2015) of these studies had data available for the meta-analysis, which showed that needle gage did not affect arterial puncture-related pain [MD -0.07, 95% CI -0.86, 0.71] (Fig. 2). The risk of bias among these studies is shown in Figure A4d, Appendix 1.

3.5.5. Ultrasound-guided procedure

Three (Bobbia et al., 2013, Grandpierre et al., 2019, Carpizo et al., 2014) studies assessed ultrasound-guided procedure compared to standard procedure and showed contrasting results. Carpizo and colleagues (Carpizo et al., 2014) found lower arterial puncture-related mean pain, better success rate at the first puncture, and less time to successful blood draw in the intervention group compared to the control group. Grandpierre and colleagues (Grandpierre et al., 2019) found lower arterial puncture-related median pain, higher success at the first attempt, and less punctures in the intervention group. Bobbia and colleagues (Bobbia et al., 2013) found no difference in arterial puncture-related median pain between the intervention and control groups, a higher number of attempts, and a higher time to successful blood draw in patients undergoing ultrasound-guided arterial puncture.

All three studies were included in the meta-analysis, which showed that ultrasound-guided procedure did not affect arterial puncture-related pain [MD -1.74, 95% CI -3.51, 0.03] (Fig. 2). The risk of bias in these studies is shown in Figure A4e, Appendix 1.

3.5.6. Topical anesthetics combined with local anesthetic infiltration

Tatli and colleagues (Tatlı et al., 2018) assessed the combined effect of 5% lidocaine cream and 1 ml of 1% lidocaine infiltration, compared to lidocaine infiltration only in 104 patients undergoing transradial catheterization. The combined intervention was associated with lower mean pain (3.7 ± 1.8 in the treatment group and 4.9 ± 2.0 in the control group, $p = 0.02$) and lower radial artery spasm (26.9% vs 9.6%, $p = 0.04$), while no differences emerged for other secondary outcomes.

3.5.7. Iontophoresis using anesthetics

Only one (Sherwin et al., 2003) small study on 30 patients undergoing radial artery cannulation explored the effectiveness of 10 min of iontophoresis prior to arterial puncture using lidocaine compared to lidocaine infiltration. No difference in arterial puncture-related mean pain or puncture attempts emerged between groups.

3.5.8. Engineered blood gas syringe and jet injector

Baskin and colleagues (Baskın et al., 2014) compared 25 gage-needle, safety-engineered blood gas syringes to 26 gage-needle conventional heparinized syringes on 550 patients undergoing blood collection for arterial blood gas analysis. No difference was observed in arterial puncture-related mean pain, puncture attempts, patients' and physicians' perceived difficulty in performing arterial puncture, or in the proportion of samples rejected by the laboratory between groups. The intervention group registered a lower number of local complications.

Hajiseyedjavady and colleagues (Hajiseyedjavady et al., 2012) compared pain levels after 0.2 ml of 2% lidocaine administered via jet injector to 1 ml of 2% lidocaine gel applied topically 5 min before arterial puncture on 41 patients who underwent blood collection for arterial blood gas analysis. The lidocaine jet injector device reduced pain (1.29 ± 0.90 vs 4.19 ± 1.43, $p<0.001$, Mann-Whitney U test) and number of attempts (1.29 ± 0.46 vs 2.1 ± 0.12, $p = 0.009$).

3.5.9. Local massage

Lasocki and colleagues (Lasocki et al., 2020) evaluated the effect of 10 min of local massage therapy in combination with EMLA™ patch compared to EMLA™ patch alone in 64 patients undergoing blood collection for arterial blood gas analysis. Local massage therapy reduced arterial puncture-related pain during (1 [IQR 0, 4] in the massage group vs 2 [IQR 0, 4] in the control group, $p = 0.04$) and after the procedure (2 [IQR 0, 4] vs 3 [IQR 1, 5], $p = 0.01$), as well as arterial puncture-related stress (0 [IQR 0, 3] vs 1 [IQR 0, 5], $p = 0.02$) and heart rate variation (-1.2 [IQR -5, 1.2] vs +1.3 [-1.3, 4.6]; $p = 0.0014$). No differences emerged in systolic blood variation or puncture attempts.

3.6. Secondary outcomes

Secondary outcomes were gathered into six main categories: 1) technical issues (*n* = 41); 2) complications and side effects (*n* = 24); 3) satisfaction and psychological issues (*n* = 22); 4) arterial puncture-related pain experience (*n* = 12); 5) biophysiological parameters (*n* = 6); and 6) costs (*n* = 2) (Table 2).

4. Discussion

This systematic review aimed to describe interventions to reduce arterial puncture-related pain and provide an estimate of their effectiveness. In addition to local anesthetic infiltration, our review identified four further main analgesic techniques, including cryotherapy, topical anesthetics, narrower needle gage, and ultrasound-guided procedure.

Our findings suggested difference among analgesic interventions. Local anesthetic infiltration provided the greatest pain reduction of 1.42 on a scale of 10. Although a decrease of at least 1.65 on a scale of 10 is recognized as the minimum needed to be defined as clinically important (Bahreini et al., 2020), this parameter is different for procedural pain. Indeed, when pain is absent before a procedure, a reduction as small as 0.5 points can still be clinically relevant for patients (Rowbotham, 2001). Included studies used both lidocaine (Matheson et al., 2014, Lightowler and Elliott, 1997, France et al., 2008, Wade et al., 2015) and mepivacaine (Giner et al., 1996) with some success, but there is still debate about the optimal dosage and concentration. Our findings contradict the common misbelief that patients exposed to local anesthetic infiltration feel pain twice because they receive two punctures (Hudson et al., 2006, Pagnucci et al., 2020). Moreover, the benefits of local anesthetic infiltration are usually rapid and last for some time (e.g., lidocaine takes effect within 2 min and the effect lasts 30 to 60 min) (Latham and Martin, 2014), thus facilitating repeated puncture if needed. After physicians, nurses are the healthcare professionals most frequently involved in performing arterial punctures. Our findings showed that nurses carried out this procedure in 11 of the 37 (30%) studies that specified the performing healthcare professional. Few nurses have prescriptive authority worldwide, and most nurses can only administer medications like local anesthesia with a physician's order (Alobayli, 2019), which may be a barrier to the use of local anesthesia before arterial puncture (Hudson et al., 2006, Alobayli, 2019). Therefore, establishing standing orders for local anesthetic infiltration as part of a standard, pre-arterial puncture protocol may help overcome concerns regarding delays due to waiting for a medical prescription. The creation of an arterial sampling kit with pre-packed local anesthetic for infiltration may be another strategy to promote the use of local anesthetic infiltration even when there are time constraints. As previously mentioned, the literature suggests that the main reasons for not using local anesthetic infiltration is lack of knowledge and training, as well as disbelief of the benefit (Valero Marco et al., 2008, Zinchenko et al., 2016, Lightowler and Elliott, 1997). Addressing these misconceptions through local educational and training sessions may help to overcome this hesitancy and promote a change in practice.

Cryotherapy also emerged as beneficial in reducing patients' perception of arterial puncture-related pain, with a mean pain reduction of 1.13 on a scale of 10. Apart from some comorbid clinical conditions, such as Raynaud's disease and scleroderma, for which cooling may have significant adverse effects (Poredos and Poredos, 2016), cryotherapy can be considered a valid alternative to local anesthetic infiltration for several reasons, including its availability, rapid effectiveness, safety, ease of application, non-invasive profile, and favorable cost-benefit ratio (McSwain and Yeager, 2015). In our studies, cryotherapy was applied for a median of 3 min before arterial puncture, thus suggesting that the additional time required for this technique is not prohibitive. Moreover, cryotherapy was found to be more economical than local anesthetic infiltration and topical anesthetics (Aaron et al., 2003, Pagnucci et al., 2020, Rüsch et al., 2017), and it can be employed in patients who are allergic to anesthetics and additives.

Our review showed limited benefit of topical anesthetics, with a mean pain reduction of 0.58 on a scale of 10. This poor benefit is likely the result of the different agents examined (i.e., tetracaine, amethocaine, and lidocaine alone or in association with prilocaine), different dosages and concentrations, forms (i.e., gel, ointment, or cream), times of application (30 to 240 min before arterial puncture), and the large variability in sample sizes. A previous review on the pharmacology of topical anesthetics suggested that depth of anesthesia depends on the contact time: the anesthetic effect has been shown to reach a maximal depth of 3 mm after 60 min of continuous application, and 5 mm after a 120 min (Kumar et al., 2015). This lengthy time of onset suggests that topical anesthetics may not be suitable for critical or emergency situations, as previously reported (Aaron et al., 2003, Pagnucci et al., 2020). Moreover, the sample size of the included studies on topical anesthetics ranged from 40 patients (Aguilar et al., 2007, Smith et al., 1990) to over 500 patients (Joly et al., 1998), thus introducing potential wide heterogeneity. Finally, skin characteristics may have an impact on the effectiveness of topical anesthetics, with the elderly experiencing the maximum effect due to a subtle epidermal layer (Mayoral et al., 2010). Only two of the 10 studies on topical anesthetics in our meta-analysis enrolled patients who were 65 or older (Latsios et al., 2017, Tran et al., 2002),

The use of a narrower needle gage did not seem to affect arterial puncture-related pain, differently from evidence in the area of venipuncture research (Mouser et al., 2017, Padoan et al., 2020). It may be postulated that fine needles increase procedural difficulty (Yee et al., 2015), since arteries are located deeper in the body than veins, thus requiring more puncture attempts. An audit of arterial blood gas analysis experience involving patients with chronic hypoxic lung disease who received long-term oxygen therapy, showed that arterial puncture-related pain increased with each attempt (Crawford, 2004). Moreover, the small number of articles that explored the impact of needle gage on arterial puncture-related pain was extremely limited and could have prevented the identification of significant effects.

Similarly, although ultrasound-guided venipuncture was associated with a lower proportion of patients reporting high pain intensity (NRS>3) (Yamagata et al., 2018), our findings did not show a reduction in arterial puncture-related pain when ultrasonography was employed. The role of operator experience on ultrasonography-related procedural outcomes is still debated (Midia et al., 2019), even if expertise is likely to have a positive impact (Yamagata et al., 2018). In our review, a reduction in arterial puncture-related pain was documented when the procedure was performed by experienced healthcare professionals (Grandpierre et al., 2019, Carpizo et al., 2014). On the other hand, in a study that investigated arterial punctures performed by a heterogeneous population of both highly trained and novice healthcare professionals, ultrasonography showed no benefit on pain reduction and an increase in the number of attempts and time to successful blood draw (Bobbia et al., 2013). In any case, we were not able to draw high-quality conclusions about the effectiveness of ultrasound-guided arterial puncture due to the limited number of studies included in this review and their high heterogeneity.

4.1. Limitations

This review provides an estimate of effectiveness for each of the main analgesic interventions aimed at reducing arterial puncture-related pain. However, our findings do not allow us to rank this effectiveness. Such ranking would have been possible in a network meta-analysis (Davies and Galla, 2021). Differently from standard pairwise meta-analyses, which compare the efficacy of two interventions that have been directly compared in clinical trials, network meta-analyses can be used to simultaneously compare any number of treatments (Davies and Galla, 2021). Network meta-analyses compare interventions using both direct comparisons of interventions within trials and indirect comparisons across trials based on a common comparator (Li et al., 2011). Although network meta-analyses may support optimal clinical decision-making in everyday practice because they assess the relative effectiveness of several interventions across a network of trials, their conclusions may be biased when there is imbalance in the distribution of clinical and methodological

characteristics, and indirect and mixed comparisons are not valid due to important differences between trials that compare aspects other than treatments (Cipriani et al., 2013). Therefore, we chose to perform a standard pairwise meta-analysis.
Secondarily, the limited number of studies for each main analgesic technique did not allow us to investigate the potential reasons for heterogeneity across the studies, which is important in all cases except local anesthetic infiltration. Moreover, the estimate of effectiveness for each analgesic intervention was affected by a generally high overall risk of bias of the studies. Finally, at least seven (García García et al., 2005, Joly et al., 1998, Mayoral et al., 2010, Russell et al., 1988, Guevara Sanz and Conde Anguita, 2001, Smith et al., 1990, Guevara Sanz and Requena Castillo, 2011) studies that were deemed valuable could not be included in the meta-analysis, because the authors did not provide additional information.

5. Conclusions

This systematic review and meta-analysis highlights the effectiveness of local anesthetic infiltration, cryotherapy, and topical anesthetics in reducing arterial puncture-related pain. Moreover, although we could not rank the interventions due to the standard pairwise meta-analysis design, our findings suggest a trend. Local anesthetic infiltration provided the greatest pain reduction; it should be considered standard practice before arterial puncture and introduced in contexts where it is not yet routine. Educational and training interventions aimed at familiarizing healthcare professionals with international guidelines about procedural pain management, as well as organizational measures that improve the provision of adequate analgesia before arterial puncture, are needed. Cryotherapy has rapid onset and may represent a safe and readily available alternative to local anesthetic infiltration when other anesthetics are lacking, or when patients have a history of allergy or hypersensitivity to anesthetics or additives. Topical anesthetics had limited benefit, and their lengthy time of onset may not be suitable for critical or emergency situations. They may be an option when particular comorbid conditions (e.g., Raynaud's disease and scleroderma) make the use of cooling impossible. High-quality conclusions are not possible for the use of narrower needle gauges and ultrasound-guided arterial puncture due to the limited number of studies included, despite encouraging preliminary evidence for the latter. Caution must be used when interpreting these results, given the high risk of biased methods in the included studies and the heterogeneity observed across studies.

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Table 1
Summary of the selected articles.

Author(s) (Country, year) Quality[*]	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Aaron et al. (Canada, 2003) Some concerns	To determine whether a topical anesthetic agent (tetracaine) provides effective local analgesia prior to radial AP.	Double-blind, randomized, placebo-controlled trial.	Pulmonary lab	I: 1 g of tetracaine gel 4% ($N = 24$) C: odorless placebo gel ($N = 26$) Gel application 45 min prior to the arterial puncture.	Pain immediately after the arterial puncture (VAS 0–100)	Successful puncture (N,%) Time to successful withdrawal (*sec*) Puncture attempts (N) Difficulty of AP as perceived by HCPs (4-point Likert scale) Skin reactions at 24 h (patient's self-report).	$N = 50$ $M = 34$ (68) Age $I = 60$ (12) Range 37–79 C = 61 (15) Range 25–86	$I = 7$ (29) C = 3 (12)	ABG	23	Yes	Respiratory therapist	(i) **higher mean (SD) pain in the intervention group compared to the control group immediately after the procedure [26.2(32.6) VS 23.8(27.4), $p = 0.78$];** (ii) no differences in the likelihood of unsuccessful puncture (1/24 intervention group VS 3/26 control group), $p = 0.61$ (iii) no differences in the time of successful blood withdrawal [70(103) intervention group VS 49(48) control group, $p = 0.40$] (iv) no differences in the number of patients requiring more than one puncture attempt [6/24 intervention group VS 4/26 control group, $p = 0.40$] (v) no differences in the degree of perceived difficulty to perform the procedure ($p = 0.86$) (vi) no differences in skin reactions among groups.
Aguilar et al. (Spain, 2007) High[a]	To evaluate the efficacy of Emla anesthetic cream for reducing pain related to radial artery puncture	Double-blind, randomized, placebo-controlled trial.	NR	I: 2 g of 2.5% lidocaine/ 2.5% prilocaine cream ($N = 20$) C: 2 g of placebo cream ($N = 20$)	AP-related pain (VAS 0–10)	Proportion of patients experiencing high pain intensity (VAS $\geq$ 2) (N,%)	$N = 40$ M = NR Age = NR	NR	ABG	NR	No	NR	**(i) No significant difference in mean (SD) pain between the intervention and the control groups [1.33 (0.8) vs 1.84 (1.3)];** (ii) Lower proportion of patients experiencing high pain intensity in the intervention group compared to the control group (5% vs 35%, $p = 0.04$).

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Ballestreros et al. (Spain, 2017) Low	To evaluate the efficacy of ethyl chloride spray versus placebo for reducing pain caused by AP.	Single-blind, randomized, placebo-controlled clinical trial.	Emergency department	I: Ethyl chloride spray applied immediately before the AP ($N = 66$). C: Vaporization of a base hydroalcoholic placebo solution ($N = 60$).	Pain immediately after the AP (NRS 0–10)	Difficulty of AP as perceived by HCPs (3-point Likert scale) Puncture attempts (N) Time to successful withdrawal (*sec*) Adverse events at 7 h	$N = 126$ $M = 79$ (63) Age $I = 67$ (14) C = 69 (12)	NR	ABG	22	Yes	Nurse	**(i) no statistically significant differences in median (IQR) pain immediately after the procedure between groups [$I = 2(1–5)$ VS C = 2(1–4.5) $p = 0.72$];** (ii) no differences in the time of successful blood withdrawal [median= 37(25–57) intervention group VS 34(30–53) control group, $p = 0.83$]; (iii) AP perceived as more painful when lasted more than 37 s ($p< 0.001$) (iv) and when experienced as difficult ($p< 0.001$); (v) no adverse events were reported.
Baskin et al. (Turkey, 2014) High	To compare easiness of use, physician-patient satisfaction, laboratory appropriateness, and complications between safety-engineered and conventional heparinized syringes used during the AP.	Open, randomized, controlled trial.	Emergency department	I: Use of a 25 G needle safety-engineered blood gas syringe ($N = 275$). C: Use of a 26 G needle conventional heparinized syringe ($N = 275$).	Pain experienced during the procedure (VAS 0–10)	Puncture attempts (N) Procedural difficulty as perceived by patients and HCPs (5-point Likert scale) Local complications after procedure and after 48 h (N) Rejection of blood samples by the laboratory (N)	$N = 550$ $M = 318$ (58) Age $I = 69$ (16) Range 17–99 C = 68 (17) Range 17–98	NR	ABG	I: 25 C: 26	Yes	Physician	**(i) no statistically significant differences in mean pain immediately after the procedure between the intervention group compared to the control group [3.03(2.4) VS 3.47(2.18)], $p = 0.14$];** (ii) no differences in the puncture attempts [1.28 (0.7) intervention group VS 1.36 (0.7) control group), $p = 0.49$; (iii) no differences in terms of the degree of difficulty according to patients ($p = 0.11$) and physicians ($p = 0.55$); (iv) significantly higher number of early local complications in control group ($p = 0.02$), mostly local pain ($p = 0.04$; (v) no differences in sample rejections among groups ($p = 0.41$).

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Bastami et al. (Iran, 2015) High	To determine the efficacy of applying ice before the AP in decreasing pain perceived during the procedure.	Open, randomized, controlled trial.	Hospital	I: 5-minute application of an ice pack before the AP. ($N = 31$) C: Standard procedure. ($N = 30$)	Pain immediately and 5 min after AP (VAS 0–10)	Heart rate (beats/min)	$N = 61$ $M = 34$ (55) Age $I = 61$ (12) C = 62 (15)	$I = 18$ (58) C = 16 (55)	ABG	25	No	Researcher experienced with the procedure	(i) **lower mean (SD) pain in the intervention group compared to the control group immediately after the procedure [3.12(1.68) VS 4.6(1.56), $p<0.001$]; lower mean (SD) pain in the intervention group compared to the control group 5 min after the procedure [1.9(1.51) VS 2.53(1.85), $p = 0.15$];** (ii) no differences in heart rates before ($p = 0.82$) and during ($p = 0.99$) the procedure among groups.
Bobbia et al. (France, 2013) Some concerns	To compare ultrasound-guided AP vs conventional procedure.	Open, randomized, controlled trial.	Hospital (Emergency department)	I: Ultrasound-guided AP ($N = 37$) C: Standard procedure ($N = 35$)	Pain experienced during the procedure (NRS 0–10)	Puncture attempts (N) Time to successful withdrawal (*sec*) Patient satisfaction (NRS 0–10) Physician satisfaction (NRS 0–10)	$N = 72$ $M = 29$ (40) Age $I = 69$ Range (56–82) C = 71 Range (61–85)	NR	ABG	NR	Yes	Physician	(i) **no statistically significant differences in median (IQR) pain experienced during the procedure between groups [3.6(2–5) intervention group VS 3.6(2–5) control group, $p = 0.9$];** (ii) higher number of attempts in the intervention group [median 2.35(1–3) VS 1.66(1–2) control group, $p = 0.17$]; (iii) higher time of successful blood withdrawal in the intervention group [132(50–200) *sec* VS 55(20–65) *sec* in the control group]; (iv) no statistically significant differences in patient and physician satisfaction among groups.

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Carpizo et al. (Spain, 2014) High	To compare the success rate at the first puncture attempt, time required, and self-reported pain between ultrasound-guided AP VS standard procedure.	Open, randomized, controlled trial.	Hospital (Emergency department)	I: Ultrasound-Guided AP ($N = 105$) C: Standard procedure ($N = 103$)	Pain during the procedure (NRS 0–10)	Success at the first puncture (%) Time to successful withdrawal (sec)	$N = 208$ $M = 120$ (57) Age $I = 74(15)$ $C = 73(16)$	NR	ABG	NR	Yes	Nurse	(i) **lower mean (SD) pain during the procedure in the intervention group compared to the control group [3.1(2.2) VS 4.7(2.6), $p<0.001$]**; (ii) better success rate at the first puncture in the intervention group [87% VS 58%, $p<0.000$]; (iii) less time to successful withdrawal in the intervention group ($p<0.001$).
Cortes-Telles et al. (Mexico, 2012) High	To determine whether topical tetracaine provides effective local analgesia prior to AP.	Single-blind, randomized, placebo-controlled trial.	Hospital (Respiratory Lab)	I: 2 g of lidocaine ointment 5% ($N = 102$) C: placebo ointment ($N = 98$) Ointment application 30 min prior to the AP	Pain immediately after procedure (VAS 0–100)	Heart rate (beats/min) Adverse events (N)	$N = 200$ $M = 95$ (57) Age $I = 57(18)$ $C = 56(18)$	NR	ABG	27	Yes	Respiratory therapist	(i) **higher mean (SD) pain in the intervention group compared to the control group immediately after the procedure [5.6(13.2) VS 6.7(14.2), $p = 0.57$];** (ii) no statistically significant differences in heart rate among groups $p = 0.89$; (iii) No adverse events were reported.
Farahmand et al. (Iran, 2017) High	To compare pain levels from ABG sampling performed with vapocoolant spray in comparison to placebo.	Double-blind, randomized, placebo-controlled trial.	Hospital (Emergency)	I: vapocoolant spray applied immediately before the AP ($N = 40$) C: placebo spray applied immediately before the AP ($N = 40$) The study agent was sprayed onto the skin from a distance of 20 cm before the resident who performed arterial puncture was present in the room by the ED attending physician. After 5 s, the site was wiped and prepared for puncture.	Pain immediately after the procedure (NRS 0–10)	Puncture attempts (N)	$N = 80$ M= NR Age $I = 56$ Range (20–76) $C = 48$ Range (19–75)	NR	ABG	23	Yes	Physician	**(i) lower mean (SD) pain in the intervention group compared to the control group [4.78(1.7) VS 4.90(1.8), $p = 0.94$];** (ii) lower number of attempts in the intervention group compared to the control group [1.38(0.5) VS 1.53(0.7)]

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Author(s) (Country, year) Quality[a]	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
France et al. (UK, 2008) High	To determine whether ethyl chloride and subcutaneous lidocaine are associated with a reduction in pain during AP compared with a standard procedure	Open, randomized, controlled trial.	Hospital (Emergency)	Group A: routine skin preparation before AP ($N = 21$) Group B: 0.5 ml of 2% lidocaine infiltration 2 min before AP ($N = 20$) Group C: vaporization of ethyl chloride spray immediately before AP ($N = 18$)	Pain during the procedure (VAS 0–100)	Puncture attempts (N) Time to successful withdrawal (*sec*)	$N = 59$ M= NR Age Group $A = 55$ Range (22–81) Group $B = 62$ Range (25–92) Group C = 57 Range (29–83)	NR	ABG	23	No	Physician	**(i) Higher mean (SD) pain in groups A and C compared to group B [$A = 23.4(11.7–35)$ VS $B = 10.2(4.8–16.3)$ VS C = 23.9(12.4–35.5];** (ii) Similar mean number of attempts ($A = 1.3$, $B = 1.2$, C = 1.1); (iii) similar mean time to successful withdrawal ($A = 65$ s, $B = 56$ s; C = 56 s).
GarcíaGarcía et al. (Spain, 2005) High[a]	To evaluate the use of anesthetic creams to relieve arterial puncture-related pain	Open, randomized, controlled trial	NR	Group 1: 2.5% lidocaine/ 2.5% prilocaine cream 30 min prior to AP ($N = 30$) Group 2: 2.5% lidocaine/ 2.5% prilocaine cream 60 min prior to AP ($N = 30$) Group 3: no intervention	AP-related pain (NR)	Patient satisfaction (NR) Skin reactions (N)	$N = 90$ M = NR Age = NR	NR	ABG	NR	No	NR	**(i) Significant pain relief in group 2 compared to group 3;** (ii) High percentage of satisfied patients that would apply the cream in another puncture in group 2 compared to group 3; (iii) No anesthetic cream-related skin reactions.

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Grandpierreet al. (France, 2008) **Low**	To compare the success at the first puncture, the number of punctures, puncture time, and patient's AP-related pain with or without US guidance.	Open, randomized, controlled trial	Hospital (Emergency medicine)	I: Ultrasound-guided procedure ($N = 36$) C: Standard procedure ($N = 37$)	Pain during the procedure (VNRS 0–10)	Success at the first puncture (%) Attempts until successful puncture (N) Time to successful withdrawal (*sec*) Physician satisfaction (VNRS 0–10)	$N = 73$ $M = 27(37)$ Age $I = 73(15)$ $C = 73(15)$	NR	ABG	23	No	Physician	**(i) lower median (IQR) pain in the intervention group compared to the control group [2(1–4) VS 6(4–8), $p<0.01$];** (ii) higher proportion of success at the first attempt in the intervention group (53 VS 19, $p = 0.01$) (iii) lower median (IQR) number of punctures in the intervention group [1(1–2) VS 3(2–6), $p<0.01$]; (iv) lower median (IQR) puncture time in the intervention group [1.4(0.6–3.1) VS 3.1(1.6–5.4), $p = 0.01$]; (v) higher median (IQR) physician's satisfaction in the intervention group compared to the control group [4(2–8) VS 8(6–9), $p = 0.01$]
Giner et al. (Spain, 1996) **High**	To quantify the pain reported by patients during AP with or without local anesthesia	Double-blind, randomized, placebo-controlled trial	Hospital (Pneumology)	Group A: Standard procedure ($N = 70$) Group B: Infiltration of 0.2 mL 1% mepivacaine hydrochloride without epinephrine ($N = 70$) Group C: Infiltration of 0.2 mL of saline solution ($N = 70$)	Pain immediately after arterial puncture (VAS 0–10)	Success at the first puncture (%)	$N = 210$ $M = 139(66)$ Age Group $A = 61(12)$ Group $B = 61(12)$ Group $C = 61(12)$	NR	ABG	22	No	Physician	**(i) lower mean (SD) pain in group B [1.5(1.5)] compared to group A [2.8(1.9), $p<0.001$] and group C [3.1(2.1), $p<0.001$];** **(iii) lower mean pain in group A compared to group C ($p = 0.44$);** (iv) no significant differences in the rate of success at the first attempt among groups [$A = 90\%$, $B = 93\%$, $C = 91\%$]

Author(s) (Country, year) Quality[a]	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Giner et al. (Spain, 1997) High	To compare pain reduction, with mepivacaine infiltration and large AP needle to narrow AP needle without prior anesthesia.	Open, randomized, controlled trial	Hospital	I: 25-gage AP needle without anesthesia ($N = 30$) C: Mepivacaine infiltration associated with 22-gage AP needle ($N = 30$)	Pain during the procedure (VAS 0–10)	Time to successful withdrawal (*sec*)	$N = 60$ M= NR Age= NR	NR	ABG	$I = 25$ C = 22	No	NR	**(i) higher mean (SD) pain in the intervention group compared to the control group [2.8(1.3) VS 1.9(1.1), $p = 0.004$];** (ii) greater mean (SD) time to successful withdrawal in the intervention group compared to the control group [158(12) vs 122(13)]
Giner et al. (Spain, 2000) High[a]	To compare pain from simple puncture of the radial artery performed with or without application of EMLA anesthetic cream and after infiltration of mepivacaine	Double-blind, randomized, placebo-controlled trial	NR	Group 1: 1 g of 2.5% lidocaine/ 2.5% prilocaine cream ($N = 51$) Group 2: 1 g of placebo cream ($N = 52$) Group 3: infiltration of 1% mepivacaine 0.2 ml ($N = 50$)	AP-related pain (VAS 0–10)	–	$N = 153$ M = NR Age = NR	NR	ABG	NR	No	NR	**(i) Significantly lower mean (SD) pain intensity in group 3 compared to group 1 [1.6 (1.8) vs 2.6 (1.8)] and group 2 [2.9 (1.8)];** (ii) No difference between group 1 and group 2.
Guevara Sanz & Conde Anguita (Spain, 2001) High	To verify the efficiency of the anesthetic ointment EMLA compared to placebo to relieve AP-related pain	Double-blind, randomized, placebo-controlled trial	NR	Group A = 2.5 g of 2.5% lidocaine/ 2.5% prilocaine cream ($N = 86$) Group B = 2.5 g of placebo cream ($N = 86$) Cream application 90 min before the procedure	Pain during the procedure (4-point Likert scale)	Pain compared to previous AP (3-point Likert scale) Difficulty of the procedure as perceived by patients (3-point Likert scale)	$N = 172$ M = 129(73) Age I = 73(8) C = 73(8)	All participants had experienced at least one previous AP	ABG	NR	No	Nurse	**(i) lower pain in the intervention group compared to the control group ($p = 0.04$);** (ii) lower pain compared to previous AP in the intervention group compared to the control group ($p<0.01$); (iii) no differences in reported difficulty of procedure among groups.

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Hajiseyedjavady et al. (Iran, 2011) **High**	To compare the level of pain during AP performed with lidocaine jet injection and lidocaine gel application	Open, randomized, controlled trial	Hospital (Emergency)	I = 0.2 mL of lidocaine 2% via jet injector (N = 21) C = 1 mL of lidocaine gel 2% applied topically (N = 21) The ABG procedure was performed 5 minutes after infiltration or application of lidocaine	Pain immediately after the procedure (VAS 0–10)	Successful attempts (N) Difficulty of procedure as perceived by physician (dichotomic scale)	N = 42 M = 25(70) Age I = 52 Range (19.85) C = 60 Range (21–89)	NR	ABG	29	No	Physician	**i) lower mean (SD) pain in the intervention group compared to the control group [1.29(0.9) VS 4.19(1.43), p<0.001];** (ii) lower number of successful attempts in the intervention group compared to the control group [1.29(0.5) VS 2.1(0.1), p = 0.009]; (iii) all physicians reported that intervention was easy (p<0.05).
Haynes (USA, 2015) **High**	To determine the efficacy of cryoanalgesia in decreasing AP-related pain.	Open, randomized, controlled trial	Hospital (Pulmonary lab)	I: Application of crushed ice to the puncture site for 3 min (N = 40) C: Standard AP procedure (N = 40)	Pain immediately after the procedure (VAS 0–100)	Success at the first puncture (N)	N = 80 M = 39 (48) Age I = 65(13) C = 64(15)	Each group was subdivided into experienced (N = 20) and naïve (N = 20)	ABG	23	No	Physician	**i) lower mean (SD) pain in the intervention group compared to the control group [13.8(17) VS 25(23), p<0.01];** (ii) lower mean (SD) pain in the naïve subgroup when ice was applied [11(14) VS 26.5(25), p = 0.02]; (iii) lower mean (SD) pain in experienced subgroup when ice was applied [15.9(19) VS 25.1(22), p = 0.15]; (iv) no differences in rate of success at the first puncture among groups (p>0.99).

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
L'Her et al. (France, 2001) High	To evaluate feasibility, tolerance, and efficacy of cryotherapy in pain reduction prior to AP	Open, randomized, controlled trial	Hospital (Emergency)	I: Application of cryotherapy 30 s prior to AP ($N = 20$) C: Standard AP procedure ($N = 20$)	Pain immediately after the procedure (VAS 0–100)	Patient comfort during procedure (3-point Likert scale) Patient satisfaction (3-point Likert scale) Nurse satisfaction of the procedure (3-point Likert scale)	$N = 40$ $M = 21(52)$ Age $I = 65(17)$ C = 65(17)	NR	ABG	NR	No	Nurse	**(i) lower mean (SD) pain in the intervention group compared to the control group [20(16) VS 32(23), $p = 0.01$];** (ii) no differences in perceived comfort among groups; (iii) 19/20 nurses satisfied with intervention procedure.
Ibrahim et al. (Singapore, 2015) Low	To compare differences in pain, hemolysis, potassium values, and procedural complications between APs performed with 29 G and 23 G needles.	Single-blind, randomized, crossover trial	Hospital (Emergency)	I: AP performed using 29 G needle ($N = 26$) C: AP performed using 23 G needle ($N = 24$)	Pain during the procedure (VAS 0–100)	Rate of hemolysis (N) Variation in potassium values (N) Adverse events (N)	$N = 49$ $M = 22$ (44) Age $I = 32(8)$ C = 32(8)	NR	ABG	$I = 29$ C = 23	No	Physician	**(i) lower mean (SD) pain in the intervention group compared to the control group [23(22) VS 39(24), $p<0.001$];** (ii) higher rate of hemolysis in the intervention group compared to the control group [109(62) VS 72(137)]; (iii) higher mean (SD) potassium values in the intervention group compared to the control group [4.6(0.7) VS 4.2(0.5), $p = 0.002$]; (vi) higher number of adverse events in the control group.

Author(s) (Country, year) Quality[a]	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Joly et al. (France 2001) High	To compare pain associated with arterial cannulation after application of the EMLA cream and subcutaneous lidocaine infiltration	Open, randomized, controlled trial	Hospital (Cardiology)	I: 2.5% lidocaine/ 2.5% prilocaine cream 120 min before AP ($N = 269$) C: Subcutaneous infiltration of 0.5–0.7 mL of 2% lidocaine 5 min before AP ($N = 269$)	Pain during the procedure (VNRS 0–10)	Need for additional local anesthetic infiltration (%) Rate of failed cannulation (%) Radial spasm (%) Time to sheath insertion (min) Adverse events (N)	$N = 538$ $M = 456$ (85) Age $I = 59$ Range (45–72) $C = 58$ Range (44–72)	NR	Catheterization	18	No	Cardiologist	**(i) lower median (IQR) pain in the intervention group compared to the control group [2(1–3) VS 7(6–8), $p = 0.0001$];** (ii) patients in the intervention group received less additional lidocaine infiltration [18(7) VS 92(34), $p<0.0001$]; (iii) lower number of failed cannulation in the intervention group compared to the control group [10(4) VS 26(10), $p = 0.006$]; (iv) lower number of radial spasms in the intervention group compared to the control group [3(1) VS 11(4), $p = 0.002$]; (v) lower median (IQR) time to sheath insertion in the intervention group compared to the control group [4(3–5) VS 6(2–12), $p = 0.0002$]; (vi) no differences in the occurrence of adverse events among groups
Khalil (Egypt, 2017) High	To assess the effect of ice pack application on pain level perceived during AP	Open, randomized, controlled trial	Hospital (Emergency)	I: Application of ice pack 10 min before AP ($N = 50$) C: Standard procedure ($N = 50$)	Pain immediately after the procedure (VAS 0–10)	Heart rate before and during the procedure (beats/min)	$N = 100$ $M = 58$ Age $I = 56(2)$ $C = 54(2)$	NR	ABG	25	No	Researcher	**(i) lower mean (SD) pain in the intervention group compared to the control group [7.36(2.1) VS 7.88(0.8), $p = 0.01$];** (ii) no differences in heart rate before the procedure ($p = 0.46$); (iii) lower heart rate during the procedure in the intervention group compared to the control group [78(11) VS 86(6), $p = 0.03$]

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	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Kim et al. (South Korea, 2007) **High**	To evaluate the effects and optimal application time of EMLA cream in relieving pain during transradial coronary procedures	Double-blind, randomized, placebo-controlled trial	Hospital (Cardiology)	Phase 1 I: Application of 2.5 g of 2.5% lidocaine/ 2.5% prilocaine cream ($N = 69$) C: Application of 2.5 g of placebo cream ($N = 73$) Creams applied 120 to 240 min before the procedure Phase 2 (5 time-range groups) I: Application of 2.5 g of 2.5% lidocaine/ 2.5% prilocaine cream 0–1 hour, 1–2 h, 2–3 h, 3–4 h, and >4 h before AP ($N = 48$, 73, 72, 45, and 59) C: Application of 2.5 g of placebo cream ($N = 98$)	Pain during the procedure (VAS 0–100; VRS-4)	Time to maximize the benefits of 2.5% lidocaine/ 2.5% prilocaine cream application	Phase 1 $N = 142$ $M = 78(55)$ Age $I = 60(10)$ C = 61(11) Phase 2 $N = 395$ $M = 223(56)$ Age $I = 60(9)$ C = 60(10)	NR	Catheterization	20	Yes	Physician	**Phase 1:** **(i) Lower mean (SD) pain in the intervention group compared to the control group [19(22) VS 49(24), $p = 0.001$ and 1.5(0.6) VS 2.3(0.5), $p = 0.001$ by using both VAS 0–100 and VRS-4, respectively];** **Phase 2:** **(i) Significant differences in mean pain between the lidocaine/prilocaine cream >1 hour groups and the control group ($p<0.05$);** (ii) No statistical differences in mean pain between lidocaine/prilocaine cream 0–1-hour group and the control group; (iii) Significant difference in mean (SD) pain between the lidocaine/prilocaine cream 1–2 h group and lidocaine/prilocaine cream >4 h groups [14(18) VS 32(24), $p<0.01$].

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	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Lasocki et al. (France, 2020) High	To evaluate the effect of massage therapy in reducing AP-related stress and pain	Open, randomized, crossover trial	Hospital (Intensive Care Unit)	I: 10-min massage therapy prior to AP ($N = 64$) C: Standard procedure ($N = 64$) All patients were exposed to lidocaine/prilocaine patch for at least 30 min prior to AP.	Pain during the procedure (NRS 0–10)	Pain immediately after the procedure (NRS 0–10) Apprehension prior to AP (NRS 0–10) Heart rate variation (%) Systolic blood pressure variation (%) Puncture attempts (N)	$N = 64$ $M = 57(76)$ Age $I = 65(15)$ $C = 65(15)$	NR	ABG	NR	No	Nurse	**(i) Lower median (IQR) pain during AP in the intervention group compared to the control group [1(0–4) VS 2(0–4), $p = 0.04$];** (ii) Lower median (IQR) pain after AP in the intervention group compared to the control group [2(0–4) VS 3(1–5), $p = 0.01$]; (iii) Lower median (IQR) apprehension prior the procedure in the intervention group compared to the control group [0(0–3) VS 1(0–5), $p = 0.02$]; (iv) Significant heart rate decrease in the intervention group compared to the control group ($p = 0.0014$); (v) no differences in systolic blood variation ($p = 0.50$) and number of puncture attempts ($p = 0.13$) between groups.

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Latsios et al. (Greece, 2017) High	To test the efficacy of EMLA cream, in comparison to lidocaine subcutaneous injection in patients undergoing transradial coronary angiography	Non-inferiority open randomized trial	Hospital (coronary angiography lab)	I: 2.5 g of lidocaine 2.5%/prilocaine 2.5% cream 30 min prior to AP ($N = 225$) C: infiltration of 2% lidocaine 1–2 ml 1 min prior to AP ($N = 219$)	Pain during AP and 30 min after sheath removal (VAS 0–10)	Puncture attempts (N) Time to successful cannulation (*sec*) Radial arterial spasm (N, by angiography or clinically) Local skin reactions at 4 h (N, patient's self-report)	$N = 444$ $M = 325$ (73.2) Age $I = 65.7$ (11.5) $C = 64.8$ (10.7)	NR	Catheterization	20	NR	Radial dedicated interventional cardiologists	**(i) no difference in mean (SD) pain intensity during and 30 min after AP between intervention and control groups [4.84 (1.0) vs 4.82 (1.2), $p = 0.83$ and 0.07 (0.5) vs 0.15 (0.6), $p = 0.11$, respectively];** (ii) similar mean (SD) number of puncture attempts between intervention and control groups [1.16 (0.7) vs 1.20 (0.4), $p = 0.32$]; (iii) no differences in the mean (SD) time to successful cannulation between intervention and control groups [62.24 (25.7) *sec* vs 64.04 (18.78) *sec*, $p = 0.40$]; (iv) no difference in radial spasm betwenn intervention and control groups (8% vs 10%, $p = 0.55$); (v) no serious skin reactions in the intervention group.

Author(s) (Country, year) Quality[a]	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Lightowler & Elliot (England, 1997) High	To compare skin infiltration with local anesthetic lignocaine before AP to infiltration with normal saline and no infiltration.	Double-blind, randomized, placebo-controlled trial	Hospital (NR)	Group 1: infiltration with 0.5 ml lignocaine 2% ($N = 33$) Group 2: infiltration with normal saline ($N = 34$) Group 3 = no infiltration ($N = 34$)	Pain during AP according to patients' and physicians' perspective (4-point Likert scale)	Pain during anesthetic infiltration (4-point Likert scale) Puncture attempts (N) Passes made (N) Procedural difficulty as perceived by HCPs (4-point Likert scale)	$N = 101$ $M = NR$ Age = NR	NR	ABG	29	No	Senior house officers in respiratory medicine	**(i) lower pain intensity during AP in lignocaine group compared to normal saline and no infiltration groups according to both patients' ($p = 0.001$ and $p = 0.024$, respectively) and physicians' perspective ($p = 0.036$ and $p = 0.011$, respectively);** (ii) no difference in pain intensity during AP between normal saline and no infiltration according to both patients' ($p = 0.7331$) and physicians' perspective ($p = 0.600$); (iii) no difference in pain intensity during infiltration with lignocaine compared to normal saline according to both patients' and physicians' perspective ($p = 0.25$); (iv) no difference in the puncture attempts ($p = 0.80$) neither in the passes made ($p = 0.74$) among groups; (v) no differences in the degree of perceived procedural difficulty ($p = 0.60$).
Mahto et al., (India, 2016) High	To determine whether cryoanalgesia could be an effective analgesic before arterial puncture and to evaluate level of pain using different needle sizes for arterial sampling	Open, randomized controlled trial	Hospital (medical intensive care unit)	I: plastic bag filled with crushed ice applied for 3 min ($N = 40$) C: no cryoanalgesia ($N = 40$) An ABG sample was drawn for both groups using a 23-G needle and the next day using a 26-G needle.	AP-related pain (VAS 0–10)	–	$N = 80$ $M = 55$ (68) Age $I = 52.6$ (16) C = 54.2 (18)	NR	ABG	23 and 26	NR	Respiratory therapist	**(i) Lower median pain when 26-G needle compared to 23-G needle was used both in the intervention group [0 (IQR 0–1) vs 2.00 (IQR 1–2), $p = 0.001$] and in the control group [1.5 (IQR 1–2) vs 4.00 (IQR 3.25–5), $p = 0.001$].**

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	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Matheson et al. (USA, 2014) **High**	To compare standard practice and three methods of analgesic infiltration to determine if one method was more successful than the others at reducing pain with the ABG needle stick	Single-blind, randomized, placebo-controlled clinical trial	Hospital (medical/surgical nursing units; or trauma intensive care units)	Group 1: infiltration of 1% lidocaine 0.7 ml ($N = 10$) Group 2: infiltration of buffered 1% lidocaine 0.7 ml ($N = 10$) Group 3: infiltration of bacteriostatic saline 0.7 ml ($N = 10$) C: no analgesic infiltration before AP ($N = 10$)	AP-related pain (VAS 0–10)	Overall AP-related pain experience (VAS 0–10)	$N = 40$ $M = 21$ (52.5) Age = 61.8 (NR)	NR	ABG	NR	Yes	Critical care nurse	**(i) Lower mean (SD) pain in the lidocaine group compared to buffered lidocaine, bacteriostatic saline and no analgesic infiltration groups [1.6 (1.5) vs 3.3 (1.0) vs 4.6 (2.3) vs 6.2 (0.4) respectively, $p = 0.001$];** (ii) Significantly less pain in buffered ($p = 0.041$) and plain lidocaine ($p < 0.001$) groups than in the non interventional group; no difference between lidocaine and bacteriostatic saline ($p = 0.665$); (iii) Lower mean (SD) pain for ABG puncture overall experience in the lidocaine group compared to buffered lidocaine, bacteriostatic saline and no analgesic infiltration groups [3.1 (2.9) vs 4.3 (3.9) vs 4.7 (2.8) vs 7.3 (1.6) respectively, $p = 0.022$]; (iv) Lower pain for overall AP-related experience in the lidocaine group compared to the non intervention group ($p = 0.017$); no difference with buffered lidocaine ($p = 0.168$) or bacteriostatic saline ($p = 0.330$).

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	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Mayoral et al. (Spain, 2010) High	To verify the efficiency of the anesthesic ointment EMLA compared to placebo to relieve AP-related pain	Double-blind, randomized, placebo-controlled trial	Hospital (NR)	I: 1 ml of lidocaine 2.5%/prilocaine 2.5% cream 30 min prior to AP ($N = 23$) C: moisturing cream 1 ml 30 min prior to AP ($N = 28$)	AP-related pain (VAS 0–10)	Procedural difficulty as perceived by patients (3-point Likert scale) Puncture attempts (N)	$N = 51$ $M = 33$ (64.7) Age = 76 (11)	NR	ABG	23	NR	Nurse	(i) No difference between groups about AP-related pain ($p = 0.78$); (ii) Correlation between procedural difficulty as perceived by patients and puncture attempts ($r = 0.6$, $p < 0.01$).
Micu et al. (France, 2006) High	To assess the efficacy of EMLA patch on pain resulting from AP performed for ABG	Single-blind, randomized, trial	Hospital (lung function laboratory)	Group 1: lidocaine/prilocaine patch 60 min prior to AP ($N = 34$) Group 2: cold cream 60 min prior to AP ($N = 31$) Group 3: no intervention ($N = 38$)	AP-related pain (VAS 0–10)	Anxiety (4-point Likert scale)	$N = 103$ $M = 70$ (68) Age Group 1 = 60 (2) Group 2 = 56 (3) Group 3 = 53 (2)	NR	ABG	26	NR	Nurse	**(i) No difference in AP-related mean pain (SD) among groups (group 1, 2 (0.3); group 2, 2.4 (0.3); and group 3, 1.8 (0.3), $p = 0.350$);** (ii) No correlation between AP-related pain and anxiety ($r = 0.21$); (iii) no relationship between AP-related pain and patients' gender ($p = 0.518$) or HCP performing AP ($p = 0.963$); (iv) AP-related pain was usually of a weak to moderate grade (≤ 4) (group 1, 31/3; group 2, 25/6; and group 3, 34/4), $p = 0.393$); (v) No correlation between pain score and previous number of AP, ranging between 0 and 5 ($r = 0.073$); (vi) No differences in anxiety score among groups ($p = 0.354$).

Author(s) (Country, year) Quality[a]	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Olday et al. (UK, 2002) High	To compare topical 4% amethocaine gel with 2% lidocaine infiltration for analgesia for radial artery cannulation	Open, randomized, controlled trial	Hospital (cath lab)	I: topical 4% amethocaine gel 60 min prior to AP (NR) C: infiltration of 2% lidocaine (0.5–0.7 ml) 1 min prior to AP (NR) Lorazepam 1–3 mg to all patients 2 h prior to AP	Pain immediately after AP (VAS 0–10)	Time to successful cannulation (*sec*)	*N* = 99 *M* = NR Age = NR	NR	Catheterization	20	Yes	Experienced registrar or consultant anesthetist	**(i) No difference in the median pain [IQR] immediately after cannulation between amethocaine and lidocaine groups (2 [0–4] vs 2 [1–3.5], *p* = 0.93);** (ii) No difference in the median time [IQR] to cannulation between amethocaine and lidocaine groups (65 [41–142] vs 59 [40–105]); (iii) Failure to cannulate in 5 patients of the amethocaine group and 7 patients of the lidocaine group ($p = 0.54$); (iv) No serious skin reactions to the amethocaine application.

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Pagnucci et al. (Italy, 2020) High	To compare three anesthetic methods (two administered topically, and one subcutaneously) with standard practice (no anesthesia) to establish whether one method was more effective than the others in reducing pain caused by radial artery puncture	Open, randomized, controlled tria	Hospital (emergency department)	Group 1: cryoanalgesia – 200 g of ice over the site for 3 min prior to AP ($N = 134$) Group 2: 2 g of lidocaine 2.5% /prilocaine 2.5% cream 60 min prior to AP ($N = 133$) Group 3: subcutaneous infiltration of mepivacaine 1 ml ($N = 135$) Group 4: no intervention ($N = 133$)	Pain during AP (NRS 0–10)	Success at the first puncture (N) AP pain > 3/10 (N) Cost per pain unit on NRS scale (€)	$N = 533$ $M = 309$ (58) Age Group 1 = 59 (30.5) Group 2 = 55 (33.1) Group 3 = 57 (31.7) Group 4 = 57 (29.2)	NR	ABG	22	Yes	Nurse certified in performing ABG	**(i) Significant lower median (IQR) pain score during AP in mepivacaine [1 (0.6–1.3), $p = 0.023$)] and cryoanalgesia groups [3 (2.0–3.9), $p = 0.012$)] compared to the control group [6 (4.0–7.0)];** **(ii) No difference in pain intensity during AP between anesthetic cream group [5 (4.2–5.9), $p = 0.861$)] and control group;** (iii) Median (IQR) pain during mepivacaine infiltration of 1 (0.4–2); (iv) Success at first puncture ≥ 95% in all groups; (v) Higher AP pain > 3 in the control group ($N = 133$, 100%) compared to anesthetic cream ($N = 120$, 90%), cryoanalgesia ($N = 29$, 22%) and mepivacaine groups ($N = 0$); (vi) Lower cost for the reduction of one unit on the NRS for cryoanalgesia (0.03 €), followed by mepivacaine (0.41 €) and anesthetic cream (3.48 €).

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Patout et al. (France, 2015) Some concerns	To compare the pain experienced during arterial punctures performed with a 25 G or 23 G needle	Double-blind, randomized trial	Hospital (respiratory ambulatory)	Group 1: 23-G needle ($N = 100$) Group 2: 25-G needle ($N = 100$)	Pain during AP (VAS 0–100)	Most painful moment of the procedure (needle insertion, during AP, after AP, repeating AP) Time to successful withdrawal (*sec*) Anxiety before and after AP (VAS 0–100)	$N = 200$ $M = 106$ Age Group 1 = 66 (13.2) Group 2 = 63.4 (15.2)	Group 1 = 79 (79) Group 2 = 78 (78)	ABG	23 and 25	Yes	Nurse certified in performing ABG	**(i) No significant difference in the median (IQR) pain experienced by patients using a 23-G needle (6.63 mm [0–19 mm]) or a 25-G needle (5.21 mm [0–18.49 mm]) ($p = 0.53$);** (ii) Pain more frequent at needle insertion in the 23-G needle group than in the 25-G needle group (60 vs 46, $p = 0.047$); (iii) Higher median (IQR) time to successful withdrawal when using the 25-G needle (42 s [35–55 s]) compared to the 23-G needle (33 s [24.5–35 s]) ($p = 0.002$); (iv) Significant decrease in the level of anxiety before and after AP in both groups (both $p < 0.001$); (v) At the multivariete analysis significant relationship between pain and anxiety prior to AP ($R^2 = 0.32$, $p < 0.001$).

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Ruetzler et al. (Austria, 2012) Low	To test the hypothesis that lidocaine/tetracaine patch analgesia is non-inferior to that provided by subcutaneous lidocaine injection for insertion of arterial catheters	Non-inferiority, double-blind, randomized, placebo-controlled trial	Hospital (cardiothoracic department)	I: heated lidocaine/tetracaine patch + saline subcutaneous infiltration ($N = 45$) C: identical-appearing unheated placebo patch + subcutaneous infiltration of 1% lidocaine 0.5 ml ($N = 45$) Patches removal after 20 min, immediately followed by infiltration of study solution and AP attempted after 3 min	Pain during AP (VAS 0–100)	Pain during infiltration of study solution (VAS 0–100) Pain 1 min after AP (VAS 0–100) Patient satisfaction (4-point Likert scale) Pain during AP as perceived by HCPs (4-point Likert scale) Puncture attempts (N) Procedural difficulty as perceived by HCPs (5-point Likert scale) Skin reactions at the patch site (5-points Likert scale)	$N = 90$ $M = 70$ (77.8) Median age (IQR) $I = 68$ (54–75) $C = 69$ (59–74)	NR	Catheterization	20	Yes	NR	**(i) No difference in the mean (SD) pain score during AP between the intervention group and the control group [26 (16) vs 29 (22)];** (ii) Lower pain score during subcutaneous infiltration in the intervention group compared to the control group ($p < 0.001$); (ii) No group differences in any other secondary outcomes, including pain after AP ($p = 0.04$), patient satisfaction (($p = 0.07$), pain as evaluated by HCPs (($p = 0.02$), puncture difficulty (($p = 0.94$), puncture attempts ($p = 0.93$, or erythema ($p = 0.080$).

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Rush et al. (Germany, 2017) High	To test the superiority of vapocoolant spray compared with lidocaine infiltration for radial artery cannulation	Single-blind, randomized, placebo-controlled trial	Hospital (anesthesia and intensive care department)	I: vapocoolant spray ($N = 74$) C: alcoholic disinfectant spray + infiltration of 2% lidocaine 0.5 ml ($N = 69$)	Overall AP-related pain experience (NRS 0–10)	Cannulation failure within 3 min (N) Time to successful cannulation (*sec*) Cost (€)	$N = 143$ $M = 62$ (43.4) Age $I = 67$ (10) $C = 68$ (8)	NR	Catheterization	20	NR	Physician	**(i) Lower mean (SD) pain in the vapocoolant group compared to the lidocaine group [3.4 (1.58) vs 4.5 (2.29), $p = 0.032$)];** (ii) Lower mean time (SD) to successful cannulation in the vapocoolant group compared to the lidocaine group [128 (44) vs 135 (44), $p = 0.019$)]; (iii) No difference in the cannulation failure rate; (iv) Total cost decreased by 18% when using vapocoolant.
Russell et al. (UK, 1988) High	To compare the efficacy of lidocaine/prilocaine emulsion with lidocaine infiltration in reducing pain associated with arterial cannulation	Open, randomized, controlled trial	Hospital (anesthesia department)	Group 1: 2.5 g of lidocaine/prilocaine emulsion 60 min prior to AP ($N = 20$) Group 2: 2.5 g of lidocaine/prilocaine emulsion 90 min prior to AP ($N = 20$) Group 3: infiltration of 1 to 2 ml of 2% lidocaine 2 min prior to AP ($N = 20$) All patients received 5 to 10 mg of diazepam orally	Pain during AP (VAS 0–100 and 4-point Likert scale)	Pain during AP as perceived by HCPs (VAS 0–10 and 4-point Likert scale) Puncture attempts (N) Skin reactions (N, HCP's assessment)	$N = 60$ $M = 30$ (50.0) Age Group 1 = 59 (7) Group 2 = 62 (9) Group 3 = 59 (9)	NR	Catheterization	17.5	NR	Physician	**(i) Lower median pain in group 2 compared to group 1 (3.5 vs 30) and group 3 (3.5 vs 22), both $p < 0.001$, according to patients' perspective;** (ii) Lower median pain in group 2 compared to group 1 (1.5 vs 9.5) and group 3 (1.5 vs 8.5), both $p < 0.01$, according to HCP's perspective; (iii) No difference between group 1 and group 3 according to both patients' and HCP's perspective; (iv) Good correlation between patients' and HCP's pain score ($r = 0.66$); (v) No difference in the puncture attempts; (vi) No severe skin reactions due to emulsion.

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Sanz (Spain, 2011) **High**	To assess the effectiveness in pain reduction by using finer needles when performing ABG	Open, randomized, controlled trial	Hospital (NR)	I: 25-G needle ($N = 86$) C: 22-G needle ($N = 86$)	AP-related pain (4-point Likert scale)	Procedural difficulty as perceived by HCPs (4-point Likert scale)	$N = 172$ $M = 124$ Age = NR	All	ABG	22 and 25	NR	Nurse	**(i) Lower pain intensity in the 25-G needle group compared to the 22-G group (absent, 60.5%vs 9.1%; mild, 31.4%vs 53.5%; severe, 9.1%vs 36.0%; untolerable 0%vs 2.3%, $p < 0.01$);** (ii) Lower procedural difficulty when using 25-G needle ($p < 0.001$).
Sherwin et al. (UK, 2003) **High**	To compare the effectiveness of lidocaine iontophoresis with that of local infiltration of lidocaine for the prevention of pain during radial artery cannulation	Single-blind, randomized, trial	Hospital (vascular surgery ward)	I: iontophoresis for 10 min prior to AP using 4% lidocaine 4 ml ($N = 15$) C: infiltration of 1% lidocaine 1 ml ($N = 15$) AP performed 1 min after removal of iontophoresis electrodes or after local infiltration	Pain during AP (VAS 0–10)	Puncture attempts (N) Skin reactions (N, HCP's assessment)	$N = 30$ $M = 25$ Age $I = 73$ (6.6) C = 70.7 (8.5)	NR	Catheterization	20	NR	NR	**(i) No difference in mean (SD) VAS pain score between the intervention group and the control group [2.3 (2.7) vs 2.2 (1.5)];** (ii) No difference in the puncture attempts ($p = 0.65$); (iii) No serious skin reactions after removal of iontophoresis.

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Smith et al. (UK, 1990) High	To assess the efficacy of EMLA cream to alleviate the pain of arterial cannulation in unpremedicated adults and to compare its analgesic action with that of infiltration with lignocaine	Double-blind, randomized, placebo-controlled trial	Hospital (NR)	Group 1: 5 g of 2.5% lignocaine/ 2.5% prilocaine cream only ($N = 10$) Group 2: 5 g of 2.5% lignocaine/ 2.5% prilocaine + infiltration of 0.9% saline 0.2–0.3 ml ($N = 10$) Group 3: 5 g of 2.5% lignocaine/ 2.5% prilocaine + infiltration of 1% lignocaine 0.2–0.3 ml ($N = 10$) Group 4: placebo cream and infiltration of 1% lignocaine 0.2–0.3 ml ($N = 10$) 2.5% lignocaine/ 2.5% prilocaine or placebo cream applied 60 min prior to AP. AP performed 2 min after infiltration or immediately after cream removal.	Pain during AP (VAS 0–10)	Pain during AP as perceived by HCPs (4-point Likert scale) Skin reactions (N, HCP's assessment)	$N = 40$ M = NR Age: 48.3 (22–69)	NR	Catheterization	20	NR	NR	**(i) Lower mean pain in groups 1, 2, and 3 than the placebo cream-lignocaine infiltration group according to patients' perspective ($p < 0.01$);** (ii) No difference in mean pain among the three 2.5% lignocaine/ 2.5% prilocaine cream groups; (iii) Similar pain scores in groups 1, 2, and 3 and significantly lower than that in group 4 according to the HCP's perspective ($p < 0.001$); (iv) No serious skin reactions in any groups.

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Tatli et al. (Turkey, 2018) High	To investigate the possible advantage of cutaneous analgesia in addition to subcutaneous administration of lidocaine before transradial access to prevent radial artery spasm	Open, randomized, controlled trial	Hospital (coronary angiography lab)	I: 5% lidocaine cream 30 min prior to AP + infiltration of lidocaine 1% 1 ml ($N = 52$) C: infiltration of lidocaine 1% 1 ml ($N = 52$) Infiltration of lidocaine 3 min prior to AP	Pain during AP (VAS 0–10)	Radial artery spasm (N, angiographycally or clinically confirmed) Access site crossover (N) Puncture attempts (N) Puncture time (time from the subcutaneous lidocaine infiltration to puncture, *sec*) Procedure time (min) Adverse events (N)	$N = 104$ $M = 72$ (69.2) Age $I = 60.5$ (9.4) $C = 60.4$ (9.7)	NR	Catheterization	20	NR	Experienced cardiologist	**(i) Lower mean (SD) pain in the intervention group compared to the control group [3.7 (1.8) vs 4.9 (2.0), $p = 0.02$];** (ii) Lower radial artery spasm in the intervention group compared to the control group (9.6% vs 26.9%, $p = 0.04$); (iii) No difference in site crossover ($p = 0.09$), puncture attempts ($p = 0.70$), puncture time ($p = 0.80$), procedure time ($p = 0.43$), vagotonia ($p = 0.06$), and vascular perforation ($p = 1.00$).
Tran et al. (Australia, 2002) High	To investigate the effectiveness of 4% amethocaine gel in reducing the pain associated with radial arterial punctures	Double-blind, randomized, placebo-controlled trial	Hospital (respiratory function laboratory, respiratory outpatients, oxygen clinic, and the respiratory ward)	I: 4% amethocaine gel 30 min prior to AP ($N = 42$) C: placebo gel ($N = 39$)	Pain during AP (VAS 0–100)	Heart rate before, during, and five min after AP (beats/min) Gel perceived as helpful (N) Desire to have the gel applied at the next AP (N) Passes made (N) Skin reactions at 24 h after AP (N)	$N = 81$ $M = 51$ (63) Age $I = 66.4$ (13.3) $C = 64.3$ (15.2)	$I = 32$ (76.2) $C = 29$ (74.4)	ABG	25	Yes	Respiratory scientists and experienced hospital medical officers	**(i) Not significant lower mean (SD) pain in the amethocaine group compared to the placebo group [16 (23.3) vs 20.7 (18.5), ($p = 0.32$);** (ii) No difference in the heart rate before, during, and after AP; proportion of patients perceiving the gel as helpful; proportion of patients eager to have the gel applied at the next AP; number of passes; and skin reactions.

Author(s) (Country, year) Quality*	Study characteristics						Study sample characteristics						Main findings
	Study aim	Design	Setting	Intervention	Primary outcome (s) investigated (assessment tool used if applicable)	Secondary outcome (s) investigated (assessment tool used if applicable)	(N) Males (%) Age, years	Previous AP N (%)	Reason for arterial puncture (catheterization vs ABG analysis)	Needle for AP (G)	Allen test (yes vs no)	Healthcare professional performing the procedure	
Wade et al. (UK, 2015) High	To evaluate the effectiveness of subcutaneous local anesthesia on the perceived pain of radial artery puncture	Open, randomized, controlled trial	Hospital (emergency department)	I: infiltration of lidocaine 1% 1 mL immediately prior to AP ($N = 20$) C: no local anesthesia ($N = 21$)	Pain during AP (VAS 0–10)	Wrist movement during AP (3-point Likert scale) Success of AP (N) Mean volume of blood obtained (SD)	$N = 41$ $M = 25$ (61) Age $I = 53.2$ (21.5) $C = 54.8$ (20.5)	NR	ABG	I: 25-G in 19 patients and 22-G in one patient C: 25-G in 18 patients and 22-G in 3 patients	Yes	Physician	**(i) No difference in median (IQR) pain between the intervention and the control groups [1.6 (0.7–3–5) vs 1.8 (0.4–5.4), $p = 0.938$];** (ii) No difference in wrist movement, success of AP, and mean volume of blood obtained; (iii) Non-significant lower median (IQR) pain in 25-G patients compared to 22-G patients [1.40 (0.40–4.30) vs 4.35 (2.30–6.95), $p = 0.150$].
Yee et al. (Australia, 2014) High	To determine whether a narrower gage needle used in ABG sampling is associated with lower pain scores and complication rates without increasing the level of difficulty of the procedure	Single-blind, randomized, trial	Hospital (emergency department)	I: 25-G needle ($N = 56$) C: 23-G needle ($N = 63$)	Pain during AP (VAS 0–10)	Successful puncture (N,%) Number of attempts (N,%) Procedural difficulty as perceived by HCPs (VAS 0–10) Local complications (N,%)	$N = 119$ $M = 61$ (51.3) Age = 64.9 (15.6)	NR	ABG	23 and 25	NR	Intern ($N = 27$, 22.7%) Senior resident medical officer ($N = 27$, 22.7%) Registrar ($N = 25$, 21%) Resident medical officer ($N = 21$, 17.6%) Consultant ($N = 7$, 5.9%) Not disclosed ($N = 12$, 10.1%)	**(i) No difference in the mean (SD) pain score between intervention and control groups [3.4 (2.7) vs 3.5 (2.7), $p = 0.81$];** (ii) No difference in successful puncture rate ($p = 1.00$), number of attempts ($p = 0.19$), and procedural difficulty ($p = 0.057$); (iii) Lower local complications rate in the 25-G needle group compared to the 23-G (5.4% vs 21.6%, $p = 0.03$).

Abbreviations: ABG, arterial blood gas; AP, arterial puncture; C, control group; I, intervention group; IQR, Interquartile range; M, male; G, gage; NRS, Numeric Rating Scale; SD, standard deviation; VAS, Visual Analogic Scale;
Note: Age was expressed as mean (SD) or range if not differently specified.
EMLA is an eutetic mixture of local anesthetics consisting in 2.5% lidocaine and 2.5% prilocaine.

*According to the Revised Cochrane risk-of-bias tool for randomized trials.

[a]Only abstracts were available

Table 2.
Secondary outcomes of included studies.

Technical issues ($n = 41$)	Complications and side effects ($n = 24$)	Satisfaction and psychological issues ($n = 22$)	Arterial puncture-related pain experience ($n = 12$)	Biophysiological parameters ($n = 6$)	Cost ($n = 2$)
Puncture attempts before successful blood collection ($n = 17$) (Aaron et al., 2003; Ballesteros-Peña et al., 2017; Baskın et al., 2014; Bobbia et al., 2013; Farahmand et al., 2017; France et al., 2008; Grandpierre et al., 2019; Hajiseyedjavady et al., 2012; Lasocki et al., 2020; Latsios et al., 2017; Lightowler and Elliott, 1997; Mayoral et al., 2010; Ruetzler et al., 2012; Russell et al., 1988; Sherwin et al., 2003; Tatlı et al., 2018; Yee et al., 2015)	Skin reactions/local complications ($n = 9$) (Aaron et al., 2003; García García et al., 2005; Latsios et al., 2017; Ruetzler et al., 2012; Russell et al., 1988; Sherwin et al., 2003; Smith et al., 1990; Tran et al., 2002; Yee et al., 2015)	Healthcare professionals' perceived difficulty with performing the procedure ($n = 8$) (Aaron et al., 2003; Ballesteros-Peña et al., 2017; Baskın et al., 2014; Guevara Sanz and Requena Castillo, 2011; Hajiseyedjavady et al., 2012; Lightowler and Elliott, 1997; Ruetzler et al., 2012; Yee et al., 2015)	Healthcare professionals' perception of patients' pain during the procedure ($n = 3$) (Ruetzler et al., 2012; Russell et al., 1988; Smith et al., 1990)	Heart rate ($n = 5$) (Bastami et al., 2015; Cortés-Télles et al., 2012; Khalil, 2017; Lasocki et al., 2020; Tran et al., 2002)	Costs ($n = 2$) (Pagnucci et al., 2020, Rüsch et al., 2017)
Time to successful blood withdrawal ($n = 8$) (Aaron et al., 2003; Ballesteros-Peña et al., 2017; Bobbia et al., 2013; Carpizo et al., 2014; France et al., 2008; Giner et al., 1997; Grandpierre et al., 2019; Patout et al., 2015)	Adverse events ($n = 6$) (Ballesteros-Peña et al., 2017; Baskın et al., 2014; Cortés-Télles et al., 2012; Ibrahim et al., 2015; Joly et al., 1998; Tatlı et al., 2018)	Patients' satisfaction ($n = 4$) (Bobbia et al., 2013; García García et al., 2005; L'Her et al., 2001; Ruetzler et al., 2012)	Patients' perception of pain immediately after the procedure or their overall pain-related experience ($n = 3$)* (Lasocki et al., 2020; Matheson et al., 2014; Ruetzler et al., 2012)	Systolic blood pressure ($n = 1$) (Lasocki et al., 2020)	
Success at the first puncture ($n = 5$) (Carpizo et al., 2014; Giner et al., 1996; Grandpierre et al., 2019; Haynes, 2015; Pagnucci et al., 2020)	Radial spasm ($n = 3$) (Joly et al., 1998; Latsios et al., 2017; Tatlı et al., 2018)	Healthcare professionals' satisfaction ($n = 3$) (Bobbia et al., 2013; Grandpierre et al., 2019; L'Her et al., 2001)	Patients' perception of pain during anesthetic or placebo infiltration ($n = 2$) (Lightowler and Elliott, 1997; Ruetzler et al., 2012)		
Time to successful cannulation ($n = 4$) (Latsios et al., 2017; Olday et al., 2002; Rüsch et al., 2017; Tatlı et al., 2018)	Rate of hemolysis ($n = 1$)(Ibrahim et al., 2015)	Patients' perceived difficulty with performing the procedure ($n = 3$) (Baskın et al., 2014; Guevara Sanz and Conde Anguita, 2001; Mayoral et al., 2010)	Proportion of patients with high pain intensity during the procedure ($n = 2$)(Aguilar et al., 2007; Pagnucci et al., 2020)		
Proportion of successful puncture ($n = 3$) (Aaron et al., 2003; Wade et al., 2015; Yee et al., 2015)	Variation in potassium values ($n = 1$)(Ibrahim et al., 2015)	Patients' anxiety ($n = 3$) (Lasocki et al., 2020; Micu et al., 2006; Patout et al., 2015)	Most painful moment of the procedure as perceived by patients ($n = 1$) (Patout et al., 2015)		
Failed cannulation ($n = 2$) (Joly et al., 1998; Rüsch et al., 2017)	Wrist movement during the procedure ($n = 1$) (Wade et al., 2015)	Patients' comfort ($n = 1$) (L'Her et al., 2001)	Patients' perceived pain compared to previous arterial punctures ($n = 1$) (Guevara Sanz and Conde Anguita, 2001)		
Withdrawn volume of blood ($n = 1$) (Wade et al., 2015)	Blood samples rejected by the laboratory ($n = 1$) (Baskın et al., 2014)				
Time to maximize the benefit of the intervention ($n = 1$) (Kim et al., 2007)	Need for additional anesthetic infiltration ($n = 1$)(Joly et al., 1998)				
	Access site crossover ($n = 1$) (Tatlı et al., 2018)				

* When pain was assessed at several time points, patients' perception of pain during the procedure was considered as primary outcome.

Fig. 1.
PRISMA flow-chart depicting the main stages of the systematic review process. aNot possible to reach three full texts thereby only the abstracts were analysed.

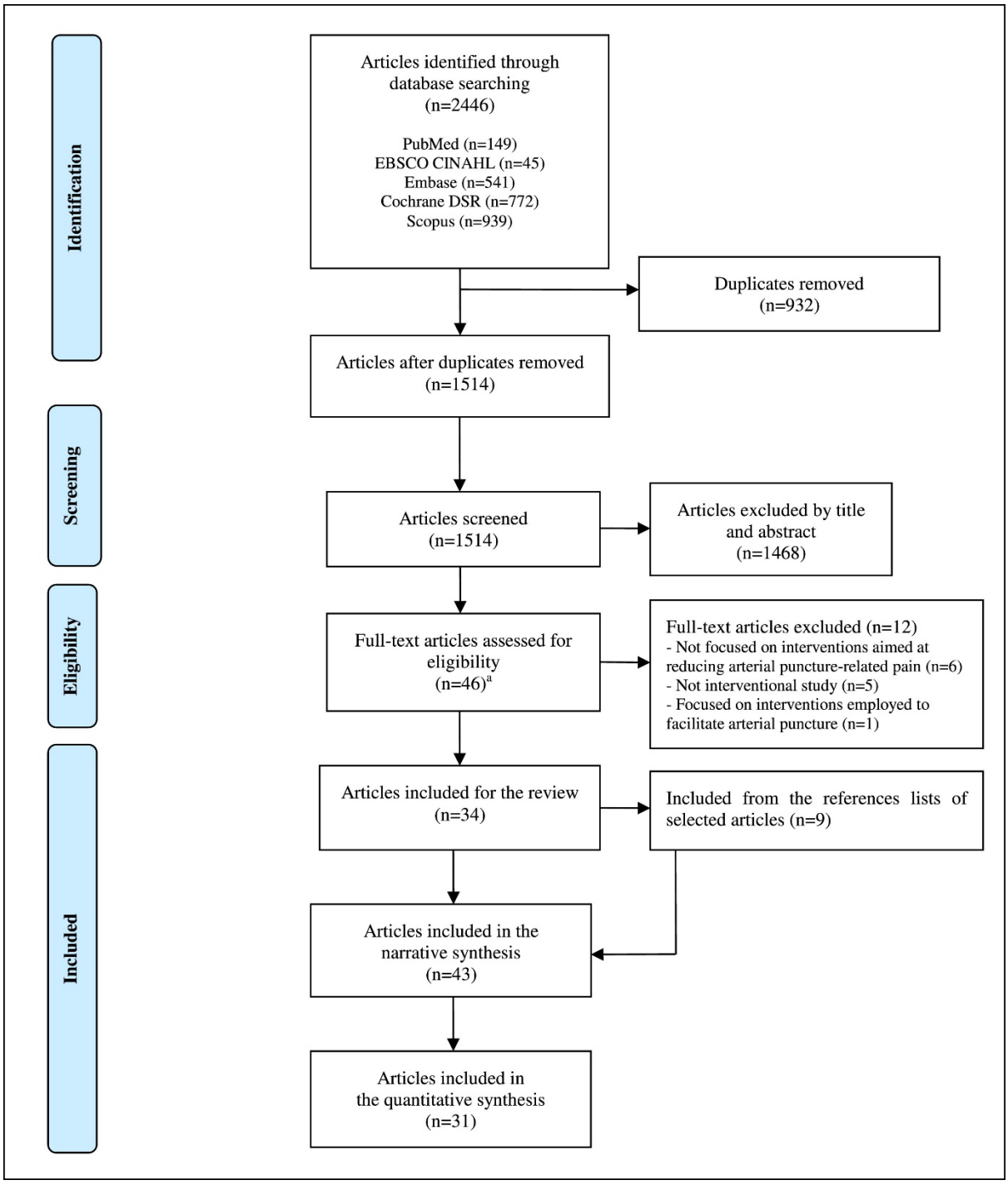
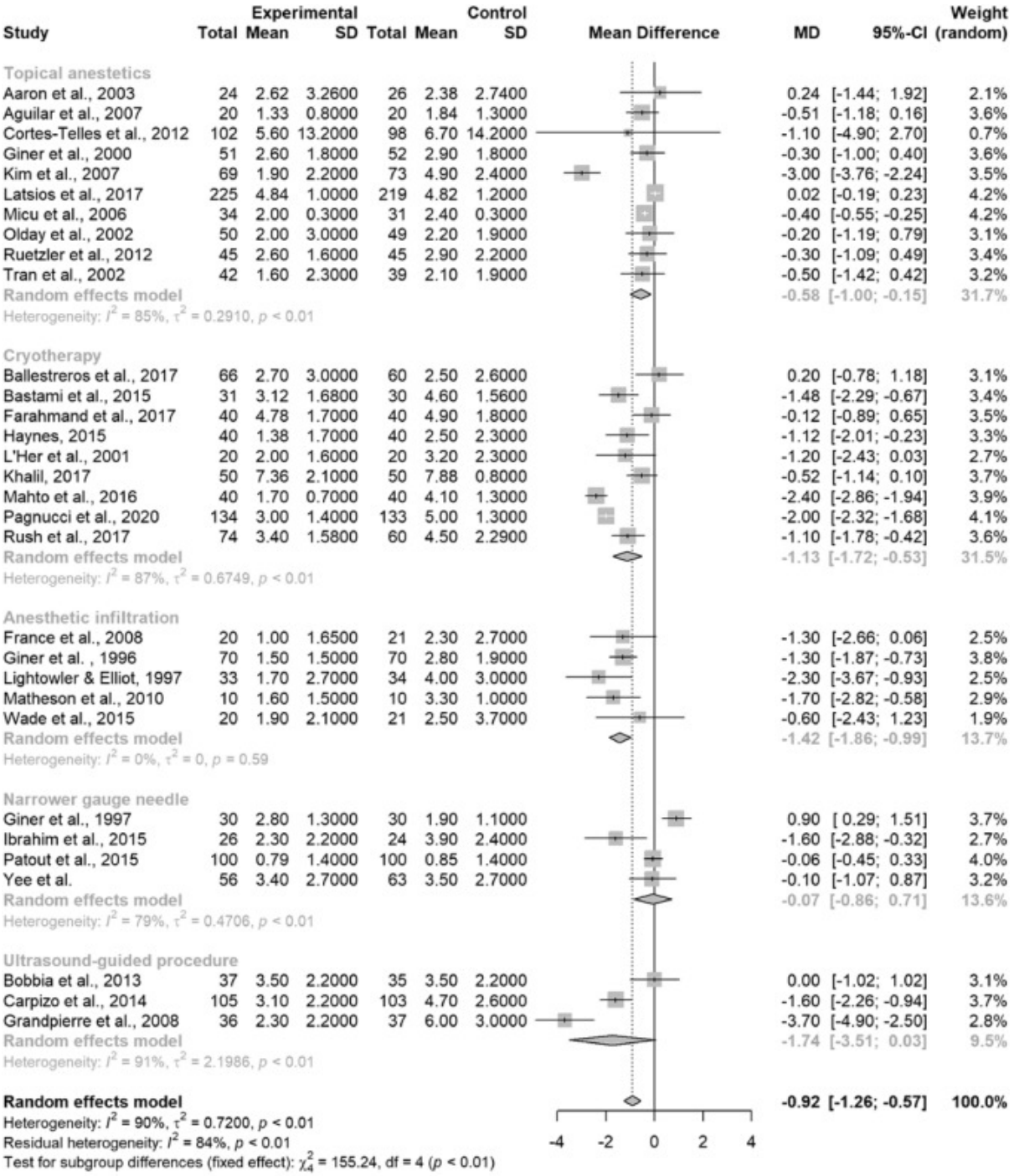


Fig. 2.
Meta-analysis of interventions to reduce arterial puncture-related pain.
Random-effects model with unrestricted maximum likelihood, with Hartung-Knapp-Sidik-Jonkman adjustment.



Random-effects model with unrestricted maximum likelihood, with Hartung-Knapp-Sidik-Jonkman adjustment.
CI, Confidence Interval; SD, Standard Deviation; MD, Mean Difference