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The effectiveness of hypnotic analgesia in the management of procedural pain in minimally invasive procedures

A systematic review and meta-analysis

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The effectiveness of hypnotic analgesia in the management of procedural pain in minimally invasive procedures: A systematic review and meta-analysis.

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None identified

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Abstract

Introduction: Patients undergoing minimally invasive procedures under a light conscious sedation perceive pain and anxiety. Hypnosis used together with analgesics has been investigated in numerous studies.

Aims and methods: This systematic review aimed to assess the effectiveness of hypnotic analgesia in management of pain, anxiety, analgesic consumption, procedure length and adverse events in adults undergoing minimally invasive procedures.

Clinical controlled trials in which hypnosis was used together with pharmacological analgesia compared to pharmacological analgesia alone during invasive procedures were included. Seven databases were searched. The methodological quality of the studies was assessed by two reviewers using a standardized instrument for critical appraisal from Joanna Briggs Institute, "Meta-Analysis of statistics assessment and review Instrument". Meta-analyses using the review manager version 5.3 software were conducted on procedure length and adverse events. Results for pain, anxiety and analgesics were synthesized in narrative summaries. Conduction of the review adheres to the

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PRISMA checklist.

Results: Ten studies comprising 1365 participants were included. A reduction in the consumption of pain medication was found between 21% and 86% without aggravating pain intensity and anxiety. In few studies significant reduction in pain intensity and anxiety was found. Meta-analysis including seven studies revealed a small beneficial effect on reducing procedure length. A meta-analysis on adverse events showed no significant reduction. Statistical heterogeneity was found among the studies included.

Conclusion: For patients undergoing invasive procedures hypnotic analgesia was effective in reducing consumption of analgesics. Only a slight effect was however found on experienced anxiety and pain intensity. It did not prolong the procedure and was safe to provide.

Relevance to clinical practice: Hypnosis is recommended as pain-management for adults during invasive procedures. A reduced consumption of pain medication potentially has a major impact on monitoring and observation of patients following the procedure, thus improving patient safety and reducing resource consumption.

What does this paper contribute to the wider global clinically community:

- A simple and inexpensive nursing intervention such as hypnotic analgesia can reduce the consumption of analgesics during a wide variety of minimally invasive procedures.
- The study findings indicate improved patient safety during and after invasive procedures because patients may require less observation

Keywords

Hypnosis; Hypnotic analgesia; Invasive medical procedure; Pain; Pain management; Visualization; Systematic review; Meta-analysis

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1. Introduction

When patients are going through minimally invasive procedures under a light conscious sedation they often experience severe pain and anxiety(Alaeddini et al., 2007; Aryana et al., 2008; Flory, Salazar, & Lang, 2007; Lang et al., 2000; Lang et al., 2006; Lang et al., 2008). A minimally invasive procedure can be defined as a procedure that is less invasive than open surgery and used for the same purpose and requires the penetration of tissue (Horne, Vatmanidis, & Careri, 1994; Wickham, 1987).

Although there are many benefits for patients from undergoing minimally invasive procedures compared with open surgery, such as smaller incisions, reduced tissue damage, faster recovery and shorter hospital stay, patients often experience pain and anxiety which sometimes can be difficult for them to manage. Factors such as a painful local anesthetic injection, an experience of more pain than expected during the procedure, alarms from the monitoring equipment, the noise from unpacking instruments and low temperature in the procedure room all affect the level of pain and anxiety in conscious patients (Baltayiannis et al., 2015). Unrelieved pain can cause distress, prolonged healing, and an extended stay in the hospital for the patients (Brennan, Carr, & Cousins, 2007). Pharmacological treatment may when given in larger doses, have potential side effects that can harm the patient and therefore have a limitation.

Hypnotic analgesia has been tested in many trials in order to reduce pain and anxiety during both medical and surgical procedures (Kendrick et al., 2016; Montgomery, David, Winkel, Silverstein, & Bovbjerg, 2002; Patterson & Jensen, 2003; Schnur, Kafer, Marcus, & Montgomery, 2008; Stoelb, Molton, Jensen, & Patterson, 2009; Tefikow et al., 2013). Invasive procedures in which hypnotic analgesia has been used together with usual pain medication with greater effectiveness compared to conventional care or usual pain medication include large core breast biopsy, percutaneous tumor treatment, radiological, percutaneous vascular, cardiovascular and renal procedures.(Flory et al., 2007; Lang et al., 2000; Lang et al., 2006; Lang et al., 2008) Besides ameliorating pain, the consumption of pain medication (Fentanyl and Midazolam) was in some studies reduced. In addition, the procedure lengths and the number of adverse events were decreased in several studies (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008).

Hypnotic analgesia is defined as:“a state of attentive and receptive concentration that allows patients to explore their own abilities to cope with a painful and distressing situation” (D. Spiegel, Bierre, & Rootenberg, 1989). Clinical hypnosis is: “ the procedure in which a person is guided by another to respond to suggestions for changes in subjective experience, alterations in perception,

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sensation, emotion, thoughts or behavior and (Green, 2003) which alters the state of consciousness, allowing for a more suggestible state, thus making it easier to change e.g. the perception of pain" (D. Spiegel et al., 1989).

Several reviews (Patterson & Jensen, 2003; Stoelb et al., 2009) and systematic reviews have been published over the years (Kendrick et al., 2016; Montgomery et al., 2002; Schnur et al., 2008; Tefikow et al., 2013) on hypnotic analgesia used together with usual care to alleviate pain and anxiety or some measures of distress from a mix of medical, surgical and invasive procedures. Based on these reviews it appeared that hypnotic analgesia is a promising non-pharmacologic adjunct treatment for ameliorating pain and surgical distress although there were significant differences between the trials which lacked clarity regarding outcomes in the various studies. Typically, these reviews have included a broad variety of surgical, medical and a few invasive procedures with patients in both general and local anesthesia.

However, two recent systematic reviews (Kendrick et al., 2016; Tefikow et al., 2013) published in 2013 and 2016 with literature searches finished in 2011 and 2013, respectively, included only randomized controlled trials and covered a broader range of medical and surgical procedures such as open surgery and a few invasive procedures. They included studies with a mixture of children and adults in the review (Kendrick et al., 2016). These factors could influence the applicability with regards to procedural pain in adult patients undergoing minimally invasive procedures. It is well-known that children respond differently to hypnosis than adults (Schnur et al., 2008; H. Spiegel, Spiegel, D., 2004). Furthermore, the reviews included studies with both patients in general anesthesia and conscious patients, even though there are obvious differences as to when and how hypnosis has to be used for pain relief in these different settings. During invasive procedures where the patient is awake, the need for hypnosis is probably greatest during the procedure where pain and anxiety are present and experienced, whereas in open surgery during general anesthesia, the need for pain relief or anxiety is pre-and postoperative. Furthermore, in the two systematic reviews only studies with interventions explicitly labeled as hypnosis were included, which may have excluded relevant studies where the intervention was labeled visualization, or guided imagery. Moreover, since the literature searches of the two systematic reviews were conducted, recent trials have probably been published, which could enhance the evidence.

Results from a new systematic review should be able to guide practitioners regarding the use of hypnosis together with usual pain medication for the reduction of pain, in conscious patients during invasive procedures and may help to identify areas for future research.

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2. Aims and methods

This present systematic review aimed to find, assess the quality and synthesize the best available evidence on the effectiveness of clinical hypnotic analgesia in the management of procedural pain in adult patients, (18 years and older) undergoing minimally invasive procedures under conscious sedation.

The review was carried out, based on a previously published protocol (Nørgaard & Pedersen, 2014). Conduction of the review adhered to PRISMA checklist for systematic reviews and meta-analyses (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). See Supplementary File 1.

2.1. Selection criteria

2.1.1. Inclusion criteria

1) Quantitative randomized or non-randomized controlled trials in English, Danish, Swedish and Norwegian were included in this review.

2) Studies with adult patients (18 years and older) who went through any kind of elective minimally invasive procedure under conscious sedation that could cause acute pain and was evaluated by patient self-report or the professional staff, were included.

3) Interventions: Studies that evaluated hypnotic analgesia (or could be labeled with hypnosis-related terms like visualization or guided imagery) provided together with usual pain medication used during minimally invasive procedures were included. Hypnosis could be provided either face-to face or as a pre-recorded version without limits on the length of the intervention.

4) Comparators in the included studies were usual analgesics or usual care typical for the institution.

5) Outcomes: Studies with the following outcome measure were included: procedural pain intensity. Additionally, studies with the following outcomes were included: patient experienced anxiety, the amount of analgesic used during the procedure, the length of the procedure, and the number of adverse events.

When assessing the outcomes, pain and anxiety validated scales were used.

2.1.2. Exclusion criteria

Studies were excluded if hypnotic analgesia had been used during open surgery, during dental procedures, during burn treatment and other non-invasive procedures. In addition, studies where hypnotic analgesia was used for children and adolescents as they represent a different population in

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this respect. Studies on hypnosis used during labor was also excluded, as a systematic review was carried out in this field in 2012 with an update in 2016.(Madden, Middleton, Cyna, Matthewson, & Jones, 2012).

2.2. Search strategy

The aim of the search strategy was to identify published and unpublished studies. The search strategy was conducted in three steps. First a limited search was made in July 2018 of MEDLINE via Pub Med and of CINAHL. An analysis was then conducted of the text words in the title and abstract and in the index terms used to describe the articles. Furthermore, an initial search in Cochrane and the JBI Library was performed for any protocols for systematic reviews in the field. In all included databases searches were then made with all the identified keywords and index terms: e.g. hypnosis, "hypnotic analgesia", "self-hypnosis", "self-hypnotic relaxation"; non pharmacological analgesia; acute pain; procedural pain, invasive procedure. Finally, the reference lists of all identified articles were searched for additional studies and cited reference searches were applied. For this review searches were carried out in databases from inceptions through July 2018. The published literature was searched in MEDLINE via PubMed, CINAHL, Scopus, Swemed+ and PsycINFO. Grey literature was searched in the following databases and websites: Mednar, ProQuest Dissertations and Theses (for international dissertations and theses), Google Scholar, Trip database, National Institute of Health's (NIH) Clinical Trials Databases (Host: http://www.clinicaltrials.gov), American Society of Clinical Hypnosis (ASCH) (Host: http://www.asch.net/), The American Board of Medical Hypnosis (ABMH) (Host: http://www.abmedhyp.net/) The American Society of Clinical and Experimental hypnosis (SCEH) (Host: http://www.sceh.us/),International Society of Hypnosis (ISH) (Host: http://www.ishhypnosis.org/). For a full search strategy in PubMed see Appendix 1.

2.2.1. Deviation from the protocol

Cochrane and JBI databases were proposed in the second search in the protocol (Nørgaard & Pedersen, 2014), but these databases are repositories of secondary research and therefore were not used in the secondary search. Furthermore Embase and Web of Science were not included in this review as described in the protocol. EMBASE is contained in Scopus and Scopus and Web of Science are almost identical. It was not possible to access, the databases "Mosby's Nursing Consult", "Expanded Academic ASAP" and "Sociological Abstracts" from Denmark.

2.3. Study selection

To exclude the non-relevant studies, all titles and abstracts found with the search strategy, were screened by the primary reviewer (MWN).

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Two reviewers independently evaluated abstracts from studies that could meet inclusion criteria in order to find studies where full text should be retrieved. Finally, the full text articles were screened against criteria for inclusion.

2.4. Quality assessment

Prior to inclusion in this review, two reviewers (MWN and PUP) independently assessed selected studies for their methodological validity. A standardized instrument for critical appraisal from Joanna Brigg Institute, Meta-Analysis of statistics assessment and review Instrument (JBI-MAStARI) was used (Institute, 2014). If there were disagreements between the reviewers a third reviewer was involved in the discussion. It was not necessary to involve a third reviewer. Two reviewers other than MWN and PUP assessed a study authored by MWN and PUP (MB and SJH). Assessment of the studies is presented in table 1.

2.5. Data extraction

Quantitative data from the included studies were extracted by two reviewers (MWN and PUP). A standardized data extraction tool from JBI-MAStARI (Institute, 2014) was used to extract data, which included specific details about the interventions, populations, methods and outcomes of significance for the review question and objectives. See table 2

2.6. Dealing with missing data

In the meta-analysis analyses were conducted that attempted to account for unobserved data. These imputed data were assessed in a sensitivity analysis to assess the potential impact on the effect size (Collaboration, 2011).
If standard deviations (SD) were missing in continuous data, imputation of SD was conducted as follows: the average of the other studies SD was used to impute missing SD (Furukawa, Barbui, Cipriani, Brambilla, & Watanabe, 2006). If data were reported as medians and interquartile range (IQR) the following approach was used: Median=mean. IQR/1.35 = SD(Collaboration, 2011).
If data were reported as mean and range, imputation of missing data was not used due to lack of robust imputation methods, which also excluded these studies in the meta-analyses.

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2.7. Data synthesis

We conducted a meta-analysis with the review manager version 5.3 software (Copenhagen: The Nordic Cochrane Centre, Cochrane). A random effects model was used to estimate the pooled effects for procedure length and adverse events outcomes. We included data from randomized controlled trials and quasi-experimental studies in the same meta-analysis. A random model effect was used because the studies differed e.g. according to sample size, type and length of invasive procedures and we expected that the treatment effect size would vary from study to study. Standardized mean difference was the effect size estimate of the meta-analysis used for procedure length, as the studies did not use the exact same outcome measure. The effect for the adverse event outcome as dichotomous data, was expressed as the Risk Ratio of an event occurring. Few studies had three randomization arms (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Shenefelt, 2013; Slack et al., 2009) but we have included only thee control and the hypnosis arms from Lang's studies, the control and the hypnosis arms with pain suggestions from Slacks' study and the control and the face to face hypnosis arms from Shenefelt's study in the meta-analysis. See table 2.

It was not possible to perform meta-analyses for the pain intensity, anxiety and consumption of pain medication outcomes because the measurements for the outcomes were assessed at different times, before and during the procedure. In some studies the measurements were performed at many time points expected to be especially painful during the procedure and in others at a few time points. Furthermore different methods were used for calculating data. According the outcome "consumption of pain medication" it was not possible to pool data since only one study (Norgaard et al., 2013) provided correct data for meta-analysis.

2.8. Assessment of heterogeneity

To test for statistical heterogeneity Tau^2 and Chi squared tests were used. A p-value of 0.05 was considered for statistical significance. To quantify inconsistency an I^2 test was used (Collaboration, 2011).

3. Results

3.1. Results of the search

This review included ten studies: nine randomized controlled studies (Hizli et al., 2015; Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang, Joyce, Spiegel, Hamilton, & Lee, 1996; Marc et al., 2008; Marc et al., 2007; Shenefelt, 2013; Slack et al., 2009) and one quasi-experimental study (Norgaard et al., 2013). No unpublished studies were included.

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A comprehensive literature search identified a total of 605 citations, of which 595 papers were excluded after thorough review of titles and abstracts against the inclusion criteria.

Ten papers in full text then met the criteria for this systematic review and were retrieved for further examination. Ten studies were included for critical appraisal using the JBI-MAStARI checklist (Hizli et al., 2015; Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Marc et al., 2008; Marc et al., 2007; Norgaard et al., 2013; Shenefelt, 2013; Slack et al., 2009) (Figure 1).

3.2. Methodological quality

None of the studies fulfilled all of the ten criteria in the critical appraisal check list, JBI-MAStARI (Table1). The majority of the studies were evaluated weak (Hizli et al., 2015; Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Norgaard et al., 2013; Shenefelt, 2013) with some studies evaluated as moderate quality (Marc et al., 2008; Marc et al., 2007; Slack et al., 2009) and the overall risk of bias across studies evaluated moderate to high (Collaboration, 2011). The two most common risks of bias among the studies were performance and detection bias, which occurred in most of the studies. The nature of the intervention prohibited blinding of the treatment to the participants and the majority of the studies had weaknesses due to the criteria about blinding of those assessing outcomes.

However, selection bias was present but minimized thus seven studies were truly randomized. (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Marc et al., 2008; Marc et al., 2007; Shenefelt, 2013). In two studies the randomization process was unclear (Hizli et al., 2015; Slack et al., 2009) and only one study was a non randomized quasi-experimental study with a control group (Norgaard et al., 2013). In all studies, the intervention and control group were similar and treated identically except for the exposure of the intervention. The outcome measures were calculated in a reliable way and proper statistical analyses were used in all ten studies.
Detailed descriptions of the interventions provided (hypnosis) were present and well described in all included studies and outcomes were clearly defined in all ten studies. Measurements and data were reported clearly and relevant statistical calculations applied, however, standard deviations (SD) and confidence intervals (CI) were missing in many studies.

Table 1: Critical appraisal of included studies (Institute, 2014).

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3.3. Description of the included studies

3.3.1 Types of settings

The studies were published between 1996 and 2015 in peer-reviewed journals and from four different countries: Six from the USA, (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Shenefelt, 2013; Slack et al., 2009) two from Canada (Marc et al., 2008; Marc et al., 2007), one from Turkey (Hizli et al., 2015) and one from Denmark (Norgaard et al., 2013).

The patients included represented a broad sample of patients undergoing minimally invasive procedures. However, no patients undergoing acute procedures were included. The minimally invasive procedures in the studies included were first trimester pregnancy termination, needle myography, biopsies, tumor treatments, angiographies, ablations and skin lesion excisions. In all studies patients were conscious during the procedure. The details of studies included are provided in Table 2 which summarizes the extractions of all studies included (n=10).

Table 2 : Extractions of included studies (Institute, 2014).

3.3.2. Types of participants

A total number of 1365 participants were involved (16-347 per study). Five studies had less than 70 participants (Hizli et al., 2015; Lang et al., 1996; Marc et al., 2007; Shenefelt, 2013; Slack et al., 2009). Twenty nine percent of participants were males. The ages of participants included varied between 18 and 94 years. Information about ethnicity was given in five studies (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Marc et al., 2008; Shenefelt, 2013). In these studies, participants were predominantly Caucasian (74-95%) with lower percentages being Black 3-21%, Asian 0-4% and Hispanic 0-4%. In one study, one Native American participated in the intervention group (Lang et al., 2000). Most studies had been conducted in the outpatient setting; only two studies included inpatients (Lang et al., 1996; Norgaard et al., 2013).

3.3.3. Interventions

Hypnotic analgesia (the intervention) was compared to standard care typical for the institution in all of the studies. In five studies (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Shenefelt, 2013; Slack et al., 2009) an extra arm in the randomization process was used, which was not included in this current review: empathetic attention behavior, recorded hypnosis or hypnosis without pain

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suggestion respectively. Duration of the intervention differed between the studies but the content of the intervention was comparable, since all studies used an induction, guided imagery with analgesia suggestions and progressive muscle relaxation. In five studies the intervention was provided peri-procedural (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Norgaard et al., 2013), in three studies the intervention started up to 20 minutes before the procedure and lasted throughout the procedure (Marc et al., 2008; Marc et al., 2007; Shenefelt, 2013) and in two studies the intervention was only provided before the procedure for 10-20 minutes and not during the procedure (Hizli et al., 2015; Slack et al., 2009). The intervention was delivered face-to-face in 90 % of the studies (Hizli et al., 2015; Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Marc et al., 2008; Marc et al., 2007; Norgaard et al., 2013; Shenefelt, 2013). In one study participants listened to a 20 minute audio program, using a CD player with headphones (Slack et al., 2009).

The intervention was provided to patients by a research assistant or an extra physician in all but one study. In one study the intervention was provided by one of the procedure nurses in the procedure room (Norgaard et al., 2013). In all studies included the provider of hypnotic relaxation was specially trained in the intervention. A written manual was used in eight of the studies (Hizli et al., 2015; Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Marc et al., 2008; Marc et al., 2007; Norgaard et al., 2013; Shenefelt, 2013). In four studies the intervention was monitored either by video or by unannounced visits by the primary investigator to enhance the fidelity of treatment administration (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Norgaard et al., 2013).

3.3.4 Outcomes

The primary outcome measure considered in this review was patient rated procedural pain intensity. In addition patient scored anxiety; the amount of analgesia used peri-procedural; the length of the procedure and the number of adverse events were analyzed.

In all ten studies the intervention was tested in order to reduce anxiety and pain intensity. In five studies, it was also tested in order to reduce the amount of analgesia used peri-procedural and the total amount of pain medication (Lang et al., 2000; Lang et al., 2008; Lang et al., 1996; Marc et al., 2008; Norgaard et al., 2013). In those studies in which the purpose was to reduce the consumption of pain medication a patient-controlled analgesia model was used. One study aimed to determine only whether the intervention could reduce the demand for Nitrous Oxide (N_20) as pain medication, with a yes or no (Marc et al., 2007).

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3.4. Meta-analysis results

3.4.1. Procedure length

In nine out of the ten studies, procedure length was assessed (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Marc et al., 2008; Marc et al., 2007; Norgaard et al., 2013; Shenefelt, 2013; Slack et al., 2009). In six studies, the length of the procedure was calculated as the time the patient stayed in the procedure room (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Marc et al., 2008; Norgaard et al., 2013), in one study procedure length was set as the time from start to end of the procedure (Slack et al., 2009) and in two studies the way the procedure time was determined was not described (Marc et al., 2007; Shenefelt, 2013).

The procedure length in the studies included varied from 16 minutes to 195 minutes. Seven studies were included in the meta-analysis performed on the procedure length outcome (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Marc et al., 2008; Marc et al., 2007; Norgaard et al., 2013; Slack et al., 2009). The objective of the meta-analysis was to provide a summary effect size to estimate the effect on reduction in procedure length when hypnosis was provided for pain reduction during the invasive procedures. No statistical heterogeneity in the procedure length outcome was found. Figure 2 shows a forest plot with presented results.

The absolute magnitude of the summary effect size was standardized (std.) mean size difference -0.25 (CI 95%: -0.41, -0.09). The result was statistically significant showing a small beneficial effect in reduction of procedure length. The CI was relatively narrow which indicates a fairly precise estimate. The result is consistent across studies. In two studies effect sizes were estimated based on approximation (Lang et al., 2000; Lang et al., 2008). One study reported data as medians and interquartile range (IQR)(Lang et al., 2008) where the approximation was used as follows: Median =mean, SD = IQR/1.35 (Collaboration, 2011). In another study SD was not reported (Lang et al., 2000). Here the average of the other studies' SD was used to impute the missing SD in this one (Furukawa et al., 2006). Subsequently a sensitivity analysis was performed without significant changes in the result.

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3.4.2. Adverse events

Five studies tested whether the intervention could reduce the number of adverse events defined as an event during the procedure which attracted the staff's attention to reestablish cardiopulmonary and hemodynamic stability (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Norgaard et al., 2013). Adverse events were, however, reported in three studies in the results section even though they did not mention adverse events as an outcome in their studies (Marc et al., 2008; Marc et al., 2007; Shenefelt, 2013).

Two studies found a significant decrease in the hemodynamic instability and O_2 de-saturation events in the hypnosis group versus the control group (Lang et al., 2000; Lang et al., 1996). No significant differences in adverse events between treatment and control group were found in four studies (Lang et al., 2006; Lang et al., 2008; Marc et al., 2007; Norgaard et al., 2013). One study reported no serious adverse events, although three hemodynamic instability episodes were observed in the hypnosis group vs. one in the standard group (Marc et al., 2008). In a study no significant difference between groups with regards to adverse events was reported. This study provided no raw data (Norgaard et al., 2013). The author was subsequently contacted and provided the raw data.

A forest plot of the outcome adverse events included seven studies (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Marc et al., 2008; Marc et al., 2007; Norgaard et al., 2013; Shenefelt, 2013) (Figure 3). The meta-analysis did not show a significant effect 0.61(CI 0.30, 1.26), p=0.18 and demonstrated a statistical heterogeneity thus implying underlying differences between the studies included. Heterogeneity: Tau^2=0.66 Chi^2=60.88 df =6 (p<0.00001). I^2=90%.

The possible sources of this heterogeneity were the length of the procedure, the type of invasive procedure, how invasive the procedure was and the length of the intervention provided. We decided not to investigate the heterogeneity further with subgroup analyses due to the few studies included in the forest plot. However, it seemed that by using hypnosis the number of adverse events was not increased.

When possible, adverse events were presented as the event rate (ER) in the control and the intervention groups. Relative risk reduction (RRR), absolute risk reduction (ARR), the number needed to treat (NNT) and relative risk (RR) were based on the ER and calculated with a confidence interval of 95% (Table 6).

Table 6: ER, RRR, ARR, NNT and RR for the outcome adverse Events.

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3.5 Narrative synthesis - Effect of interventions

3.5.1. Patient rated pain intensity

Results were calculated and reported differently even though nine out of ten studies used the same validated instrument to assess pain intensity; a VAS scale 0-10 or 0-100. In one study pain intensity was assessed by Subjective Units of Discomfort scale (SUD)(Shenefelt, 2013).

Results of patient rated pain intensity were difficult to summarize because the pain was measured at different times, before and during the procedure, ranging from prior to the procedure to after the intervention (Hizli et al., 2015), to every 10 minutes (Lang et al., 2006; Shenefelt, 2013), every 15 minutes (Lang et al., 2000; Lang et al., 2008; Norgaard et al., 2013), every 20 - 40 minutes (Lang et al., 1996), to rating four specific pain episodes in the procedure (Marc et al., 2008; Marc et al., 2007) and to scoring the average and worst pain post procedure (Slack et al., 2009).

In eight individually studies (Lang et al., 2000; Lang et al., 2006; Lang et al., 1996; Marc et al., 2008; Marc et al., 2007; Norgaard et al., 2013; Shenefelt, 2013; Slack et al., 2009) no statistical significant differences in patient rated pain intensity between control and intervention group in general were found.

Although the effect of hypnotic analgesia differed between the studies included and no overall effect was obtained, it appeared that there was a positive and statistical significant treatment effect on the patients' experienced pain intensity at times during the invasive procedures. See table 3

Table 3: Pain intensity measurements

3.5.2. Consumption of pain medication used

In five out of ten studies the amount of Fentanyl and Midazolam (pain medication) used peri-procedural was measured as an outcome and was calculated to be significantly less in the intervention group compared to the control group (Lang et al., 2000; Lang et al., 2008; Lang et al., 1996; Marc et al., 2008; Norgaard et al., 2013). In all but one study the results were reported without standard deviations (Norgaard et al., 2013), precluding a meta-analysis. However, to get an impression of the practical significance of the differences in consumption of pain medication between the control and intervention groups an average percentage difference was calculated

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(Table 4).The consumption of pain medication was reduced between 21% and 86 % in these five indiviadual studies.

In one study patients could choose to manage their pain with N_20 (Marc et al., 2007), where 36 % (CI 95% 16-61) of patients in the hypnosis group chose N_20 sedation peri-procedural compared to 87 % (CI 95 % 61-97) in the control group,($p<0.01$).

Table 4: Consumption of pain medication used

3.5.3. Patient rated anxiety

Anxiety was assessed by self-reporting on a VAS scale (0-10 or 0-100) at different times, pre-, during and post-procedure in eight studies but the results for procedural anxiety were reported differently (Lang et al., 2000; Lang et al., 2006; Lang et al., 2008; Lang et al., 1996; Marc et al., 2008; Marc et al., 2007; Norgaard et al., 2013; Slack et al., 2009). In one study anxiety was assessed using the Subjective Units of Discomfort scale (SUD)(Shenefelt, 2013) and in another anxiety was measured pre-procedure using the Hamilton Anxiety Scales (HAS) and Beck Anxiety Inventory (BAI) (Hizli et al., 2015).

In six out of ten studies no significant difference in anxiety in general was found between the groups (Lang et al., 2000; Lang et al., 2006; Lang et al., 1996; Marc et al., 2007; Norgaard et al., 2013; Slack et al., 2009). However, it seems that hypnotic analgesia had a positive effect on anxiety at times during some invasive procedures. See Table 5.

Table 5: Anxiety measurements

4. Discussion

The evidence was evaluated for the effectiveness of clinical hypnotic analgesia in the management of procedural pain intensity, anxiety, length of the procedure, the number of adverse events and amount of analgesics used peri-procedural in adults undergoing minimally invasive procedures. The available evidence from nine RCT's and one non-RCT suggested that hypnotic analgesia was effective in reducing consumption of analgesics. However the effect on pain intensity and anxiety was limited. Hypnosis did not prolong the procedure and was safe to provide.

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Procedure length and adverse events

By performing a meta-analysis with seven included studies, a slight statistical effect was found in reduction on procedure length. However in two studies approximation methods were used to estimate the effect size, thus encouraging a cautious interpretation of them. A sensitivity analysis was conducted and it seemed that the conclusion of the analysis was robust even though two of the seven studies included contained imputed values (Collaboration, 2011; Russo, 2007). Thus the finding was also in line with previous systematic reviews where hypnosis was used during invasive procedures to manage pain and anxiety (Kendrick et al., 2016; Tefikow et al., 2013).

From both a patient perspective and from the clinical decision makers' point of view, the most important aspect of this outcome measure was that the procedure length was not increased and therefore the intervention did not cause a consumption of extra resources. However, in only one study (Norgaard et al., 2013) the intervention was provided by the usual staff without extra resources, whereas in the other studies there was an additional person providing the intervention, which could potentially affect the procedure time by reducing it and affect the overall result.

A forest plot generated on the adverse events outcome showed a clinical and statistical heterogeneity wherefore meta-analysis was omitted (Collaboration, 2011; Russo, 2007). In most of the studies in which numbers of adverse events were measured they were defined as all episodes that could occur during the procedure requiring extra medical attention including; hemodynamic instability; oxygen de-saturation; blood pressure fluctuations; vasovagal episodes; cardiac events; etc., whereas in other studies adverse events were limited to events such as vomiting; bleeding from access site; over sedation and distracting behavior. This made it potentially difficult to compare adverse events across the studies and could be one of the reasons why previous systematic reviews have not dealt with this outcome, although it is important to investigate when an intervention is to be implemented. Indeed, in the current review, a considerable difference was found in the numbers of adverse events in the included studies, varying between 0 and 80% in the intervention group and between 1% and 96 % in the control group. This could probably be related both to how adverse events were defined and counted but also to the type and duration of the invasive procedure performed. Nevertheless, it seemed that adverse events were not increased by using hypnosis during minimally invasive procedures suggesting that hypnotic analgesia is safe to use which is a clinically relevant result in relation to patient safety.

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Pain intensity, medication consumption and anxiety

In all ten studies in this review, the results of patient rated pain intensity and anxiety outcome were reported but were difficult to compare because the measurements were assessed at different times, before and during the procedure. In some studies the measurements were performed at many time points during the procedure and in others at a few time points expected to be especially painful. In addition, different methods were used for calculating data: average pain; pain measurements as slopes obtained from a per-subject regression analysis and calculation of worst pain experienced. Therefore meta-analyses were not performed in the present systematic review. The differences described were also found in previous systematic reviews of hypnosis for pain relief in diagnostic or medical procedures (Cheseaux, De Saint Lager, & Walder, 2014; Kendrick et al., 2016).

On the primary outcome, patient-rated pain intensity and on anxiety in general no significant differences were reported between groups in most of the studies. However, in some studies trends were described in terms of a reduction of pain intensity and anxiety at time points during the procedures. By contrast a previous meta-analysis (Schnur et al., 2008) showed an overall large effect size of 0.88 (95% CI: 0.67 - 1.19), $p < 0.00001$ on reduction of emotional distress (including anxiety) with hypnosis used during the procedures. This meta-analysis predominantly included studies with hypnosis used during surgical procedures and with hypnosis studied on children. Children had a significantly greater effect from hypnosis than adults. Importantly, emotional distress was for the most part measured preoperatively thus, in most of the studies included, hypnosis was used in patients undergoing open surgery in general anesthesia. It might therefore be difficult to compare hypnosis used during invasive procedures with hypnosis used during open surgery in patients under general anesthesia. Although little effect was found on pain intensity and anxiety in five studies in this systematic review significantly less pain medication was required in the hypnosis group compared to the control group with reductions of between 21 and 86 %. In all studies in which the patients had access to intravenous pain medication, they had the same access to it throughout the procedure because they were supplied with a push button, to give the nurse a sign if they needed more pain medication. That is, the patients could control the quantity of pain medication they wanted. In the studies in which pain medication was reduced the intervention was provided face to face. Because the consumption of analgesics was significantly reduced in several studies without a significant overall change of the patients' perception of pain intensity, one could ascribe the effect of hypnosis more to the management of the pain than to affecting the intensity of pain. In line with this, previous research has shown a different effect of hypnosis on the sensitive and/or the affective pain, respectively. However, whether this difference could be attributed to analgesic suggestions

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targeting one or the other type of pain is discussed (Kendrick et al., 2016; Patterson & Jensen, 2003). This phenomenon could be one reason why, in several studies, pain intensity was not significantly altered by the intervention. A one-dimensional instrument was used to measure pain intensity in the studies included in the present review and it might therefore be difficult to observe an effect. This challenge was also described in a previous review (Kendrick et al., 2016) and points towards an important issue; that the outcomes of the interventions should be measured with tools that can capture the phenomena in question. Otherwise an effective intervention could be rejected. A recent study found that patients using hypnosis during an invasive procedure experienced pain, but the use of hypnosis helped them manage the pain by focusing away from the pain. It could therefore not be measured as a reduction in pain intensity (Norgaard, Pedersen, & Bjerrum, 2018). Nonetheless an average reduction in the amount of pain medication ranging between 21%-86% is considerable both from the patients' point of view but also from the clinician's in terms of patient safety. Thus hypnosis appears as an attractive option for patient pain management, although one should interpret the results with caution due to risk of performance bias since the participants were not blinded to the intervention.

A previous systematic review including meta-analyses (n= 34 RCT studies)(Tefikow et al., 2013) reported a significant effect in reducing pain (Hedges g = 0.44, CI: 0.26; 0.61) which with reference to the conventional values defined by Cohen (Cohen, 1962) might be interpreted as a medium effect size. Heterogeneity was however found, (X^2 = 101, 47; df =25 p<0.001; I^2= 75, 4%). This review included studies in which hypnosis was investigated in a wider range of medical and surgical procedures including both medical, open surgery and invasive procedures and studies of both children and adults in both general and local anesthesia. However, how and when this effect on pain was calculated and with how many studies included was not transparent. Ten out of 34 studies included in the present systematic review investigated patients in general anesthesia. Only six studies investigated hypnosis in percutaneous interventions. One could assume that in these studies pain was measured pre- and post-operatively due to the obvious fact that pain is experienced differently depending on whether you are awake during a procedure or in general anesthesia. It does not make sense to only measure pain prior to a procedure with a conscious patient. In addition, in this meta-analysis effect sizes were partly estimated by approximation methods on several studies due to insufficiently reported information in the studies included which might increase the risk of attrition bias in the result in this meta-analysis (Collaboration, 2011; Puhan, Soesilo, Guyatt, & Schunemann, 2006).

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4.1. Strength and limitations

4.1.2 Strength

It is strength of this systematic review that an adequate and comprehensive literature search was conducted in recognized databases using specified search terms and in collaboration with a research librarian. Furthermore, this review has been performed with rigorous methods using validated instruments (Pearson, Wiechula, Court, & Lockwood, 2005) by two reviewers and with transparency about selection and assessment of studies, and with a detailed description of the extraction of the outcome parameters from each study.

In addition it is strength that we included both randomized and quasi-experimental studies in order to find the best available research and that we investigated hypnotic analgesia in both adult in- and outpatients in hospitals in a wide range of invasive procedures, both in terms of length and degree of invasive procedure with similar results.

4.1.3. Limitations

The search differed slightly from the previously published protocol (Nørgaard & Pedersen, 2014). However, many major databases were searched and therefore the changes described should not influence the result of the search. On the other hand it cannot be excluded that we might have missed studies by not having access to these smaller databases. To minimize publication bias we did a comprehensive search for unpublished or gray literature (Collaboration, 2011) without finding any. We might have missed some relevant unpublished studies or dissertations during the iterative literature search. Moreover, a restriction to studies in English, Danish, Swedish and Norwegian language may have left out potentially relevant studies in other languages.

In non-randomized studies, there is a greater risk of selection bias and confounding factors. In addition, inclusion of non-randomized studies in meta-analyses may lead to overestimation of effect size (Collaboration, 2011). Furthermore, because of the nature of the intervention, blinding of the intervention to the participants could not be completed in nine of ten studies. That might cause a risk of performance and detection bias for the outcomes in the studies and might have affected the results in a more positive direction.

With the purpose of obtaining a more accurate estimate of the effect of hypnotic analgesia on pain and anxiety during invasive procedures, inclusion criteria with relation to the population and type of procedure or treatment were limited in this present systematic review compared to other recent

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reviews in the field (Cheseaux et al., 2014; Kendrick et al., 2016; Stoelb et al., 2009; Tefikow et al., 2013). We included adults, 18 years and older, who had undergone a minimally invasive procedure in a conscious sedation. Thereby we excluded hypnosis used during open surgery, in the management of labor pain, hypnosis used in dental settings and hypnosis used in non-invasive procedures. Limited inclusion criteria might provide a greater possibility of finding studies that asked a similar research question and a greater possibility of combining studies in meta-analyses. That could strengthen the validity of outcomes and the results' usefulness in clinical practice. The use of hypnosis together with usual pain medication must be fundamentally different depending on whether the patients are undergoing open surgery in general anesthesia or are conscious undergoing invasive procedures. Therefore, by only including studies in which hypnosis has been used during invasive procedures, generalization of the results would be strengthened. On the other hand, applying these limited inclusion criteria could compromise generalizabiliy to a greater population (Bartolucci, 2010). Although the inclusion criteria were restricted to minimally invasive procedures in this review, we could not perform meta-analyses on several outcomes as was originally planned in the protocol (Nørgaard & Pedersen, 2014). In the studies included the procedures differed as to their degree of invasiveness and duration. Moreover general variations in levels and extent of pain and measurements of pain throughout the procedure were observed, all of which might pose different requirements for the intervention and comparison of the studies. In view of this it could be difficult to generalize results to cover all minimally invasive procedures.

The large study population was predominantly Caucasian women mostly from western countries which might also compromise generalizability, warranting further research in hypnotic analgesia in relation to gender - and culture differences. There is a lack of major studies on the potential difference between women and men in the experience of the effect of hypnosis and the hypnotizibility when used to relieve pain (Green & Lynn, 2011), and that should be a subject for future research.

4.2 Implications for research

The quantitative results of the present review did not capture the way the patients experienced the intervention or whether they found it meaningful and useful – a relevant issue for further research.

Results from qualitative studies would be valuable in explaining quantitative results from studies in the field. There is a need for mixed method design studies which can complement results from rigorous qualitative and quantitative studies and provide a more comprehensive

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understanding of the research question than either quantitative or qualitative approaches alone.

Future research must be precise in definitions and the reporting of outcomes and the methods and tools used to measure the outcomes must be comparable.

Further research is required in the form of large, well-designed controlled trials, randomized or quasi-experimental studies to evaluate whether hypnosis is effective for pain management during invasive procedures.

Another relevant recommendation is that future research should think more about carrying out studies which are not conducted in a way fundamentally different from the clinical reality, where ideal resources and conditions are not always present and where implementation of results from ideal controlled and randomized studies may not be feasible. In other words there is a need to focus more on studies in which effectiveness is the goal rather than efficacy (Pearson, Wiechula, Court, & Lockwood, 2007; Rothwell, 2005).

Development of new tools designed to assess outcomes from interventions such as hypnosis could be a topic for further research. Measuring of outcome data is imperative to continually improve intervention strategies.

To fully examine the effectiveness of hypnosis during minimally invasive procedures, further research is needed to evaluate the effect of potential moderators such as participants' expectations of hypnosis, hypnotizability, and dose of hypnosis during a procedure.

5. Conclusion

The results of this review generate evidence supporting the use of hypnotic analgesia together with usual analgesics to manage pain during minimally invasive procedures. Despite the finding that hypnosis only has a limited effect on the primary pain intensity outcome and on the anxiety outcome; consumption of analgesics was reduced significantly between 21% and 86%. That provides improved patient safety because the patient may require less observation. Hypnosis does not prolong the duration of minimally invasive procedures and has no side effects.

The results of this systematic review are very valuable and can provide guidance regarding future study design and research; however, due to risk of bias in the studies, results have to be interpreted with precaution.

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6. Relevance to clinical practice

Interventions with hypnotic analgesia in a face to face form provided from a manual before, and/or during the procedure should be suitable to a wide variety and large number of patients going through minimally invasive procedures. The provider of the intervention needs to be trained in hypnotic analgesia.

Although there was clinical and statistical heterogeneity in the included studies in this systematic review, it appears that hypnosis can be useful together with the analgesics provided during invasive procedures. Based on the present review it is not possible to recommend the duration of the hypnosis session. It does not look as if patients become pain free, but their need for pain medication may be reduced significantly without increasing the experience of pain and anxiety when hypnosis is used before or/and during the invasive procedure. A reduced consumption of strong pain medication has an important impact on observation and monitoring of the patient after the procedure, thus improving patient safety and reducing resource consumption. Hypnosis does not prolong the procedure and is safe without side effects for the patients.

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Figure legends

Figure 1, PRISMA, flow diagram summarizing study selection (Moher et al., 2009).

Figure 2, Forest plot of the summary estimate of the effect of reduction in procedure length.

Figure 3, Forest plot of the summary estimate of the effect of reduction in adverse events.

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Table 1

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Lang EV et al. 2000	Y	U	Y	Y	N	Y	Y	Y	Y	Y
Marc I et al. 2007	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Slack D et al. 2009	U	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hizli F et al. 2015	U	N	N	Y	N	Y	Y	Y	Y	Y
Marc I et al.2008	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Lang EV et al. 2008	Y	N	Y	Y	N	Y	Y	Y	Y	Y
Lang EV et al. 2006	Y	N	Y	Y	N	Y	Y	Y	Y	Y
Lang EV et al.1996	Y	N	Y	Y	N	Y	Y	Y	Y	Y
Shenefelt PD. 2013	Y	U	Y	N	U	Y	Y	Y	Y	Y
Nørgaard MW et al 2013	N/A	N	N/A	Y	N	Y	Y	Y	Y	Y

Y= Yes; N= NO; U = Unclear; N/A= Not Applicable

Q1: Was the assignment to treatment groups truly random? – Selection bias

Q2: Were participants blinded to treatment allocation? – Performance bias

Q3: Was allocation to treatment groups concealed to the allocator? – Selection bias

Q4: Were the outcomes of people who withdrew described and included in the analysis?

Q5: Were those assessing outcomes blind to treatment allocation? – Detection bias

Q6: Were the control and treatment groups comparable at entry?

Q7: Were groups treated identically other than for the named interventions? – Performance bias

Q8: Were outcomes measured in the same way for all groups?

Q9: Were outcomes measured in a reliable way?

Q10: Was appropriate statistical analysis used?

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Table 2

Study	Design	Participants	Intervention A	Intervention B	Notes
Lang et al., USA 2000	RCT with three arms – Standard/Empathy/Hypnosis. Randomization using envelopes to assign participants.	241 in- and day-patients, 47% men, age 18-92 (median 56). 94% Caucasian,5% Black, 0% Asian, 1% other, 0% Hispanic undergoing per-cutaneous trans-catheter diagnostic and therapeutic peripheral vascular and renal Interventions.	Self hypnotic relaxation together with empathic attentive behavior included eight key components standardized and provided by additional person during the procedure. + provider training + manual Access to intravenous analgesia with Fentanyl and Midazolam in units (25µgFentanyl plus 0.5 mg Midazolam counted as one unit) + patient push button to require pain medication	Usual care typical for the institution. Patients attended by the department ´s special-procedure nurses, who were instructed to abstain from induction of imagery and hypnosis Access to intravenous analgesia with Fentanyl and Midazolam in units (25µgFentanyl plus 0.5 mg Midazolam counted as one unit) + patient push button to require pain medication	A second intervention group with empathic attentive behavior not included in this review Outcomes: Pain intensity; anxiety; consumption of pain medication; length of procedure time; numbers of adverse events Instrument: NRS (0-10) every 15 min. (pain and anxiety) No significant difference in patient rated pain intensity but pain increased linearly over time in standard group. Instrument: NRS (0-10) every 15 min. No significant difference in anxiety, but a decrease in anxiety in all groups over time and significant difference in slope between hypnosis and standard care group

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Study	Design	Participants	Intervention A	Intervention B	Notes
					Instrument: NRS every 15 min. Significantly reduction in procedure length in hypnosis group Significantly less pain medication in the hypnosis group. Significant lower numbers of adverse events in the hypnosis group
Lang et al., USA 2008	RCT with three arms – Standard/Empathy/Hypnosis. Randomization using random numbers in sealed envelopes	201 adult, 36, 8% men, age 29-79 (median 50). 74% Caucasian, 21% Black, 4% Asian, 1% other, 0% Hispanic under-going percuta-neous tumor treatment by transcatheter emboli-zation or RF ablation.	Self hypnotic relaxation together with empathic attentive behavior included eight key components standardized guided by additional research-assistant during the procedure + provider training + manual Access to intravenous analgesia with Fentanyl and Midazolam in units (25µgFentanyl plus 0.5 mg Midazolam counted as one unit)	Usual care typical for the institution. Access to intravenous analgesia with Fentanyl and Midazolam in units (25µgFentanyl plus 0.5 mg Midazolam counted as one unit) + patient push button to require pain medication + use of local anesthetic	A second intervention group with empathic attentive behavior not included in this review Outcomes: Pain intensity; anxiety; consumption of pain medication; length of procedure time; numbers of adverse events. Instrument: NRS (0-10) every 15 min. (pain and anxiety) Instrument for baseline anxiety: Beck's anxiety inventory)

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Study	Design	Participants	Intervention A	Intervention B	Notes
			+ patient push button to require pain medication + use of local anesthetic		Pain intensity was significantly lower from 15-30 min. and 30-45 min. interval in hypnosis group Anxiety decreased significantly in hypnosis group in the first 15-30 min and from 30-45 min. Significantly less pain medication used in the hypnosis group. No significant difference in procedure length Showed a trend toward less adverse events in hypnosis group, but not significant.
Lang et al., USA 1996	RCT with 2 arms: standard/hypnosis. Randomization using envelopes to assign participants	30 in-patients all males, ages 44-83 (66,5 mean), race not described) undergoing interventional radiologic procedures, diagnostic arteriogram, transcatheter revascu-larizations, cholecy-stomy, abcess rainage,	Hypnosis with combined elements of relaxation training and guided imagery for induction of a self-hypnotic process by a dedicated practitioner during the procedure Provider training not described.	Usual Care typical for the Institution Access to intravenous analgesia with Fentanyl and Midazolam + patient pushbutton to require pain medication + use of local	Outcomes: Pain intensity anxiety; consumption of pain medication; length of procedure time; numbers of adverse events. Instrument: NRS 0-10 at baseline, at 20 min. into every 40 min. interval (pain and anxiety)

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Study	Design	Participants	Intervention A	Intervention B	Notes
		gastrojejunostomy and nephrostomy.	No manual Access to intravenous analgesia with Fentanyl and Midazolam in units (25µgFentanyl plus 0.5 mg Midazolam counted as one unit) + patient pushbutton to require pain medication + use of local anesthetic .	anesthetic	Instrument for baseline anxiety: Beck's anxiety inventory) Pain was significantly lower rated in hypnosis group. No difference in Anxiety Significantly less pain medication used in the hypnosis group. Oxygen de-saturation reduced in hypnosis group No significant difference in procedure length
Lang et al., USA 2006	RCT with three arms – Standard/Empathy/Hypnosis. Randomization using computer generated envelopes to assign participants	A total of 236 out-patients, all but one women, age 18-94 (median 49). 80% Caucasian11% Black, 4% Asian, 1% other, 4% Hispanic undergoing large core needle breast biopsy.	Self hypnotic relaxation together with empathic attentive behavior included eight key components standardized guided by additional research assistant during the procedure + provider training + manual No pain medication used but local	Usual care typical for the institution; No pain medication used but local anesthetic	A second intervention group with empathic attentive behavior not included in this review Outcomes: Pain intensity anxiety; length of procedure time (the time the patient occupied the procedure room); total numbers of adverse events. Instrument: NRS (0-10)

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Study	Design	Participants	Intervention A	Intervention B	Notes
			anesthetic		every 10 min. (pain and anxiety) Instrument for baseline anxiety: Spielberger State Anxiety Questionaire) Pain increased more slowly over time in the hypnosis group Anxiety decreased more over time in hypnosis group No significant difference in procedure length. No significant difference in the number of adverse events
Marc et al., Canada, 2008	RCT with 2 arms: standard/hypnotic relaxation. Computer block (2 and 4) randomization used to assign participants by a statistician	A cohort of 350 outpatients, all French-spoken women, age 26.3, SD 6.3 (18-46) in the intervention group and 24.2, SD 5.0 (18-40) in the control Group, undergoing 1. trimester surgical abortion (>6< 14 weeks gestation) with	Hypnotic relaxation Session 20 minutes before the procedure and throughout the procedure guided by 1 of 2 hypnotherapists. + provider training + manual Access to intravenous analgesia with Fentanyl and Midazolam	Usual care typical for the institution – stayed 20 min. in their rooms with a relative or friend Access to intravenous analgesia with Fentanyl and Midazolam in doses (75µg Fentanyl and 2 mg Midazolam	Outcomes: Pain intensity Total amount of pain medication used; (Length of procedure time (the procedure time and the total time the patient occupied the procedure room); Instrument (pain and anxiety) NRS 0-100 at four time points during

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Study	Design	Participants	Intervention A	Intervention B	Notes
		paracervical block. 94 % Caucasian.	Midazolam in doses (75µg Fentanyl and 2 mg Midazolam initially, additional doses 25µg Fentanyl and/or 1 mg Midazolam + Patient push button to require pain medication	initially, additional doses 25µg Fentanyl and/or 1 mg Midazolam + Patient push button to require pain medication.	the procedure. Baseline: Anger, fear and sadness NRS 0-100. After 20 minutes of hypnotic induction, anxiety levels were significantly lower in the hypnotic group at the start of the procedure. Otherwise no differences in pain and anxiety between the two groups. Significantly less pain medication used in the hypnosis group. No differences in the duration of the procedure and the total time spent in the procedure room between the 2 groups.
Marc et al., Canada 2007	RCT with 2 arms: standard/hypnosis. Block randomization (six and four) using sealed envelopes to assign participants	A total of 30 out-patients, all women age 27.0 ± 7.2 in hypnosis group and 25.6 ± 4.9 in control group under-going elective first-trimester abortion (>6< 14 weeks gestation)	Hypnotic relaxation session 20 minutes before the procedure and throughout the procedure guided by hypnotist practitioner + provider training + manual	Usual care typical for the institution – stayed 20 min. in their rooms with a relative or friend. The family planning nurse was available to provide attention to	A small sample size (preliminary) study. Outcome: Request of N_2O (yes or no). Secondary: pain intensity and anxiety Instrument: NRS (0-10) at four time point during

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Study	Design	Participants	Intervention A	Intervention B	Notes
		Race not described.	Patient push button to require pain medication – not described Access to N_2O + local anesthesia used	the patient during those 20 min. Patient push button to require pain medication not described Access to N_2O. + local anesthesia used	procedure. (pain and anxiety) Instrument for baseline anxiety: Spielberger State- trait Anxiety Questionnaire) Results: Reduction in the request for N_2O in hypnosis group. No differences in pain and anxiety between groups
Slack et al.USA 2009	RCT with three arms: Audioversions: Standard/hypnotic with analgesic sugges-tions/hypnotic without analgesic suggestions. Randomization process not described Physicians blinded to randomizations scheme	26 out patients, 65.4 % male. Age 51 (SD 6) in standard care group age 56 (SD 15) in hypnotic control group and age 53 (SD 12) in the hypnotic analgesia undergoing needle electromyography (EMG) to rule out the diagnosis of either cervical or lumbo-sacral radiculopathy. Race not described.	Listened to an audio program (using CD player and head-phones. 20 minutes in duration with hypnotic induction with analgesic suggestion just before the procedure No provider training No manual No patient push button No access to pain medication Use of local anesthetics not	The standard care condition (EDU) was an audio version of the educational booklet provided to patients before the procedure. Patients listened to the audio program using CD player and head-phones 20 minutes in duration just before the procedure No access to pain medication	A second intervention group with hypnotic without analgesic suggestions not included in this review Outcomes: Worst pain, average pain; Procedure time (from first needle through skin to removal last needle) Instrument: VAS 100-mm (pain and anxiety) No significant difference between groups in pain intensity (worst pain lower in hypnosis group,

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Study	Design	Participants	Intervention A	Intervention B	Notes
			described.		but not significant) No significant difference in anxiety, but lower anxiety in hypnosis group No significant difference in procedure length between groups
Shenefelt, USA 2013	RCT with three arms – Standard/recorded hypnosis induction/ Live hypnosis induction. Randomization using computer generated pre-printed sealed envelopes to assign participants	39 out-patients, 97 % Caucasian and 3 % black people, 59% male, age 59.2 (23-75) in the live hypnosis group, age 55.9 (32-72) in the recorded hypnosis group and age 66.1 (48-76) in the control group undergoing dermato-logic surgery for removal of benign or malignant skin lesions. Skin lesions excised for the Groups included basal cell carcinoma, squamous cell carcinoma, dysplastic nevus, and cysts.	Hypnotic induction followed by self- guided imagery from the start and throughout of the procedure. A trained physician read the hypnosis script and guided the patient + provider training + manual Access to intravenous analgesia with Fentanyl and Midazolam – not described. Patient push button to require pain medication not described	Usual care `typical for the institution Access to intravenous analgesia with Fentanyl and Midazolam – not described Patient push button to require pain medication not described	A second intervention group with recorded hypnotic induction not included in this review Outcomes: Pain intensity and anxiety Instrument: SUD scale every 10 min. Anxiety was significantly reduced in the live induction hypnosis group compared to control group. No significant difference in pain between groups The numbers of participants in each group still having dermatologic surgery was too low by 30 minutes to have large enough numbers for meaningful

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Study	Design	Participants	Intervention A	Intervention B	Notes
					statistical analysis.
Hizli et al., Turke 2015	RCT with two arms, Control- and hypnosis group Randomization process not described.	64 out-patients, race not described 100% male, age 63.5 ± 6.1 in the Intervention Group and 61.8 ± 6.8 in the Control Group under-going transrectal ultrasound-guided prostate needle biopsy	The hypnosis sessions were standardized to last 10 min. before the procedure guided by a physician + manual Provider and provider training was not described Use of local anesthetic not described.	Usual Care for the institution	Outcomes: Pain intensity and anxiety. Instruments: VAS 0-10 (pain and anxiety) post intervention and before procedure Baseline anxiety: Becks anxiety inventory and Hamiltons anxiety score) Significantly less pain pre-surgery (post intervention) in hypnosis group. Significant lower anxiety pre surgery in hypnosis group. Otherwise no difference
Norgaard et al., Denmark 2013	Quasi-experimental with a control and an intervention group	147 adult in- patients, Ethnicity 100 % Caucasians undergoing RF Ablation of AF Intervention group, (n=76), 71% male, age 59, 9 ± 8.1. Control Group (n=71), 66 % male, age 59.5 ± 9.8	Structured attentive behavior together with standardized guidance to self-hypnotic rela-xation. Structured attentive behavior included eight standardized key A procedure nurse provided the	Usual care typical for the institution. The nurse who was responsible for the care of the patient was close to the patient throughout the procedure The nurses were told to do their best to	Outcomes: Pain intensity; Patients spontaneously reported pain; anxiety; numbers of adverse events and procedure length (the time the patient occupied the procedure room). Instrument: NRS every 15 minutes (pain and

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Study	Design	Participants	Intervention A	Intervention B	Notes
			intervention the patient during the procedure + provider training + manual Access to intravenous analgesia with Fentanyl and Midazolam from the departments' instructions + Patient push button to require pain medication + use of local anesthesia.	comfort the patient throughout the procedure, but to abstain from induction of visualization. Access to intravenous analgesia with Fentanyl and Midazolam from the departments' instructions + Patient push button to require pain medication + use of local	anxiety) Baseline anxiety: Symptom Checklist 92 No difference in perception of pain intensity, but the patients spontaneously expressed pain significantly less numbers of times outside the scheduled measure-ments in the intervention group. No difference in anxiety Significantly less pain medication used in the hypnosis group. No significant difference in numbers of adverse events and procedure length

Note: RCT= Randomized controlled trial; µg= microgram; mg= milligram; SD= standard deviation; NRS= Numeric Rating Scale; SUD= Subjective Units of Distress Scale; VAS= Visual Analog Scale

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Table 3

Study	Pain measurement	IG	CG	P value
Norgaard et al 2013	Number of spontaneous expressed pain (mean ± SD)	1.4 ±1.2	2.8± 1.8	0.008
	Pain intensity, NRS 0-10 every 15 min.			NS
Lang et al. 1996	Pain intensity NRS 0-10 every 20min median			
	Time average rating	1.2 (1.0-8.3)	2.5 (1.0-6.3)	NS
	Max average rating	2.0 (0-10.0)	5.0(2.0-9.0)	P<0.01
Lang et al. 2000	Pain intensity, NRS 0-10 every 15 min and calculation in slopes	slope=0·03, p=0·234 no increase in pain score	Slope=0·09 p<0·0001 increase in pain score	
Lang et al. 2006	Pain intensity, NRS 0-10 every 10 min. and calculation in slopes	Slope 0.34 p<0·0001 increase in pain score	Slope= 0.53 p<0·0001 increase in pain score	
Lang et al. 2008	Pain intensity, NRS 0-10 every 15 min and calculation in slopes median (IQR)			NS all other measurements
	15-30 min.	0(0-2)	1 (0-3)	0.02
	30 -45 min	0(0-2)	2(0-4)	0.02
Marc et al. 2007	Pain intensity NRS 0-10			
	Pain I			
	Pain II			NS
	Pain III			
	Pain IV			
Marc et al. 2008	Pain intensity (VAS 0-100, mean ± SD)			
	Pain I	11.8±17.4	12.9±17.4	NS
	Pain II	9.9± 17.0	13.6±19.0	
	Pain III	39.7±25.4	42.1± 27.9	
	Pain IV	14.4±19.5	16.2±20.3	
Shenefeldt 2013	Pain (SUD) every 10 min.			NS
Slack et al. 2009	Worst pain	49± 30	67± 25	0.049
	Average pain (VAS 0-100 mm) mean ±SD	25± 22	35± 26	0.277
Hizli et al. 2015	Pain intensity (VAS 0-10 mm) mean (range) post intervention, pre-procedure	1 (0-8)	3 (0-9)	0.011

Note: IG= intervention group; CG = control group; NRS= Numeric Rating Scale; VAS= Visual analog scale; IQR= the interquartile range; NS= Non significant; SD= standard deviation; SUD= Subjective Units of Distress Scale

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Table 4

Study	IG Fentanyl µg / Midazolam mg	CG Fentanyl µg / Midazolam mg	P Value	Relative reduction of average amount of medication used
Lang 2008 (Lang et al.,2008)	Mean 50(25-100) / 1(0,50-2)	75 (37.50-125) / 1.5(0,75-2.50)	0.0147	33%/33%
Lang 2000 (Lang et al., 2000)	Mean 22.50 / 0.45	Mean 47,50 / 0,95	<0.0001	53%/53%
Lang 1996 (Lang et al., 1996)	Mean 7(0-75) / 0.14 (0-1.50)	Mean 50.39 (0-1.25) / 1.05(0-2.50)	<0.01	86%/86%
Norgaard 2013 (Norgaard et al., 2013)	Mean 220.70±93 (SD) / 0	Mean 292±107(SD) / 0	<0.0001	24%
Marc 2008 (Marc et al., 2008)	Mean 39,39 / 1.08	Mean 49,71 / 1,62	<0.0001	21% /33%

Note: IG= intervention group; CG= control group; SD = standard deviation; µg= microgram; mg= milligram

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Table 5

Study	Anxiety measurement	IG	CG	P value
Norgaard et al 2013	Anxiety NRS 0-10 every 15 min. and after potentially painful episodes			NS
Lang et al. 1996	Anxiety NRS 0-10 every 20min median			
	Time average rating	1.2 (1.0-8.3)	2.5 (1.0-6.3)	NS
	Max average rating	2.0 (0-10.0)	5.0(2.0-9.0)	P<0.01
Lang et al. 2000	Anxiety, NRS 0-10 every 15 min and calculation in slopes	slope=-0.11 p<0.0001 decrease in anxiety score	slope=-0·04 p=0.0013 decrease in anxiety score	P=0.0022
Lang et al. 2006	Anxiety, NRS 0-10 every 10 min. and calculation in slopes	Slope- 0.27 p<0·0001 decrease in anxiety score	slope= 0.18 p<0·0001 increase in anxiety	
Lang et al. 2008	Anxiety, NRS 0-10 every 15 min, median (IQR)			NS all other measurements
	15-30 min.	2(0-4)	3 (0-5)	0.016
	30 -45 min	0(0-3)	2 (0-4)	0.015
Marc et al. 2007	Anxiety NRS 0-10 after four potential painful episodes			
	Anxiety I			
	Anxiety II			NS
	Anxiety III			
	Anxiety IV			
Marc et al. 2008	Anxiety (VAS 0-100, mean ± SD) after four potential painful episodes			
	Anxiety I	40.6 ± 29.7	38.7 ± 30.0	
	Anxiety II	34.0 ± 27.1	48.4 ± 29.8	NS
	Anxiety III	34.3 ± 27.4	33.1 ± 27.6	
	Anxiety IV	4.7 ± 9.7	7.3 ± 15.0	
Shenefeldt 2013	Anxiety (SUD) every 10 min.			NS
Slack et al. 2009	Anxiety (average) (VAS 0-100 mm) mean ±SD	33± 25	44± 41	0.432
Hizli et al. 2015	Anxiety, post intervention, pre procedure	2 (0-23)	8(0-34)	0.001
	BAI and HAS	6(0-22)	11.5 (1-38)	0.005

Note: IG= intervention group; CG = control group; NRS= Numeric Rating Scale; VAS= Visual analog scale; IQR= the interquartile range; NS= Non significant; SD= standard deviation; SUD= Subjective Units of Distress Scale; BAI= Becks anxiety inventory; HAS= Hamilton anxiety scale

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Table 6

Study	**Event rate** N (%) IG/CG	**Relative risk reduction**	**Absolute risk reduction**	**Number needed to treat**	**Relative risk** (CI 95%)
Lang 2008	8/66 (12%) 18/70 (26%)	0.53	0.14	7	0.47 (0.22-1.01)
Lang 2000	22/82 (27%) 76/79 (96%)	0.72	0.69	1	0.28 (0.19-0.40)
Lang 2006	3/78 (4%) 7/76 (9%)	0.58	0.05	19	0.42 (0.11-1.50)
Marc 2008	3/172 (2%) 2/175 (1%)	-0.53	-0.01	171 (harm)	1.51 (0.26-8.97)
Marc 2007	0/14 (0%) 1/15 (7%)	0.64	0.07	17	0.36 (0.016-8.07)
Shenefelt 2013	8/13 (62%) 8/13 (62%)	0.0	0.0	infinity	1.0 (0.55-1.84)
Norgaard 2013	61/76 (80%) 58/71 (82%)	0.02	0.02	50	1.08 (0.55-2.1)

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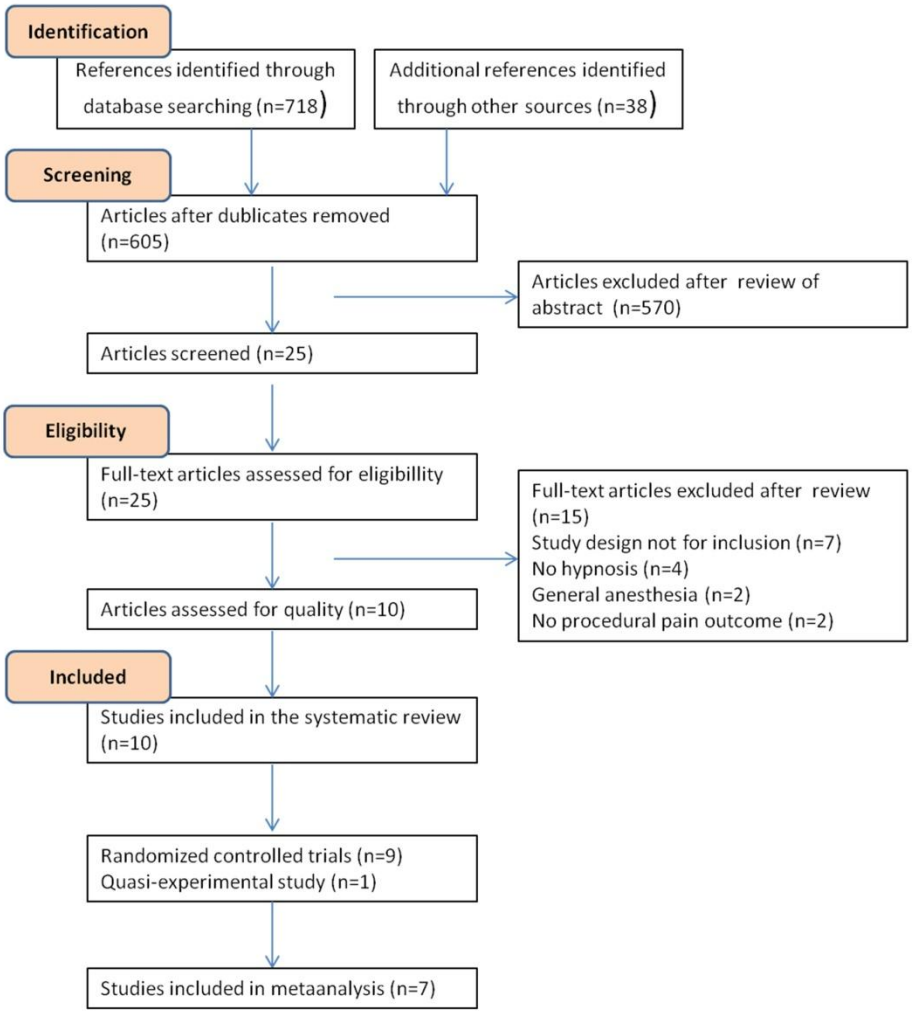

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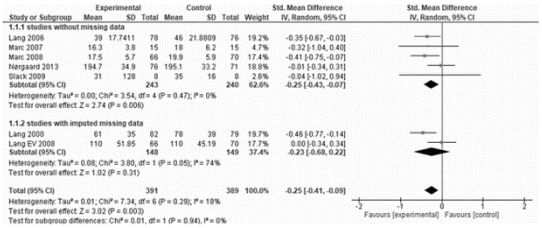

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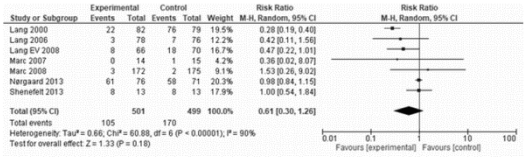

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