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REVIEW /*Interventional imaging*

Sedation and analgesia in interventional radiology: Where do we stand, where are we heading and why does it matter?

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Analgesia;
Sedation;
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Abstract The aims of this review were to describe the rationale and the techniques of sedation in interventional radiology, and to compile the safety and efficacy results available so far in the literature. A systematic MEDLINE/PubMed literature search was performed. Preliminary results from several studies demonstrated the feasibility, the efficacy and the safety of using sedative techniques in interventional radiology. Beyond pharmacological sedation and clinical hypnosis, digital sedation could reduce the anxiety and pain associated with interventional radiology procedures.

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Introduction

Interventional radiology (IR) is a medical specialty offering diagnostic and therapeutic minimally invasive procedures. In the oncologic field, the so-called interventional oncology (IO) allows to manage some issues related to cancer [1]. The concept unifying all the IR procedures is the imaging guidance which means that an adequate environment is mandatory, that can be located outside operative rooms. Percutaneous biopsies are widely performed for the diagnosis of various conditions [2]. Furthermore, interventional treatments include techniques allowing to provide local control or symptoms relief such as infiltration, ablations or cementoplasty [3—7]. In addition of interventional radiologists, these techniques raise the interest of a growing community of physicians including surgeons, anesthesiologists and organ specialists.

However, these minimally invasive procedures remain a potential source of anxiety and pain for patients [8]. Since pain is often felt when the material is inserted percutaneously, local anesthesia is routinely performed [9,10]. Additional management of acute pain and anxiety associated with medical procedures remains a major health care

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challenge. Although anesthesiologists are best trained, they are not available to attend all IR procedures. In the meantime, IR needs to understand safety considerations and to receive proper training as sedation carries significant risks for the patient [11—13]. Moreover, to improve overall patient experience in IR during the course of a disease, it is now mandatory to reconcile the desire of these patients to be more autonomous with regard to their care, and that of IR teams to prevent and effectively reduce pain and anxiety [8].

The aims of this review are to describe the rationale and the techniques of sedation in IR, and to compile the safety and efficacy results available thus far in the literature.

Material and methods

A systematic MEDLINE/PubMed literature search was performed with different combinations of terms as ''analgesia'', ''anxiety'', ''digital sedation'', ''clinical hypnosis'', ''interventional radiology'', ''local anesthesia'', ''pain'', ''sedation'', ''virtual reality''. Time period included articles published between January 2000 and August 2019. Original articles were selected based on their clinical relevance. Cited references from selected articles were analyzed to find and include significant papers previously excluded from the search or that did not come to initial attention.

Definition of sedation and analgesia

Sedation refers to the use of pharmacological and nonpharmacological means to depress the central nervous system [14]. Sedation decreases awareness and responsiveness to external stimuli [15]. The overall purpose of sedation is to reduce patient anxiety and irritability using anxiolysis, which corresponds to a state of diminished apprehension, and eventually amnesia, which refers to a loss of memory of events. Although sedation is a continuum, four levels of sedation have been categorized by the American Society of Anesthesiologists: minimal anxiolysis/sedation, moderate sedation, deep sedation and general anesthesia (Table 1) [16]. Analgesia is defined as relief of pain without intentional production of an altered mental state such as sedation. Pain signals are received, but medication prevents the perception of pain. Sedation and analgesia are distinct processes: some patients require primarily sedation, such as uncooperative patients, some primarily analgesia, and some both of them. Both must be combined in case of painful procedures because sedation alone in the presence of pain may cause confusion and restlessness. Moreover, some preclinical studies have demonstrated the possibility of the sedative hypnotic drugs to increase pain perception, or its intensity, requiring thus analgesia. However, sedation can have an analgesic effect as pain is the result of an integrated sensory, affective, motivational system that modulates nociceptive input. Analgesics such as opioids may also have a sedative effect.

Protocols of sedation and analgesia are highly variable among institutions and teams. Some routes and techniques are summarized in Table 2. There is a need of means for IR to provide each individual patient with adequate analgesia, sedation, anxiolysis, and amnesia of painful diagnostic or therapeutic procedures; to increase patient comfort; to control unwanted motor behavior that may disturb image-guided interventions; to rapidly return the patient to a state of consciousness; to minimize the risks of complications [10,17]. In IR, moderate sedation/analgesia is often considered as the ideal compromise by preserving patient cooperation, comfort, and procedural workflow similar as local anesthesia while reducing medication levels and length of the procedure compared to general anesthesia (Fig. 1) [18]. This approach allows performing a wide range of procedures that are not routinely supervised by an anesthesiologist such as biopsies, infiltrations, embolization, angioplasty, percutaneous ablation or cementoplasty. At this level of sedation, a depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation is observed (Table 1). Airway patency and spontaneous ventilation are maintained as well as cardiovascular function. Moderate sedation provides sufficient anxiolysis and control of unwanted patients' movements for most IR cases, and respiratory compromise is rare. Deeper sedation, which corresponds to a higher depression of consciousness, is discouraged because of the risks of airway and respiratory compromise. It would require the presence of an anesthesiologist. All staff members responsible for the administration of sedation and analgesia and monitoring must be able to recognize and acting on complications of over-sedation [16]. Safety checklists including sedation requisite might now be used like the one presented in Table 3 [19—22]. Appropriate equipment and drugs required for cardiopulmonary resuscitation and airway support should be available in the area where sedation is conducted.

Radiologist-controlled drug sedation and analgesia

Interventional radiologists may use a combination of drugs before, during and after the procedure to decrease pain and anxiety, thus allowing the procedure to be performed often on an outpatient basis. Table 4 summarized some means available in routine. An anxiolytic (diazepam) may be prescribed before the procedure. Local anesthesia is obtained at the site of the intervention by injecting lidocaine and ropivacaine while intravenous injection of paracetamol, nefopam or tramadol provides systemic effect. Neutralizing lidocaine with 8.4% sodium bicarbonate decreases the pain of subcutaneous injection due to the high acidity of lidocaine [23]. However, there is a spectrum of toxicities of lidocaine as the serum level increases from paresthesia to cardiovascular collapse. Thus, a maximal dose of lidocaine of 20 mg is often recommended. The duration of action of ropivacaine is considerably longer, making it more effective during the postprocedure period, even at a lower concentration than lidocaine. Antiemetics (ondansetron) are recommended with analgesics to avoid discomfort and vomiting related to analgesics. Moreover, nonsteroidal anti-inflammatory or steroidal drugs with an acid suppressing drug (omeprazole) are frequently used in association with

Table 1 Levels of sedation according to the American Society of Anesthesiologists.

	Minimal sedation	Moderate sedation	Deep sedation	General anesthesia
Responsiveness	Normal responses to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response following repeated or painful stimulation	Unarousable, even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired
Required competences	Interventional radiologist Assistant to procedure	Interventional radiologist Trained assistant to monitor patient Assistant to procedure	Interventional radiologist Dedicated sedation-trained anesthetist or alternatively an appropriately trained healthcare professional Assistant to procedure	Interventional radiologist Dedicated sedation-trained anesthetist or alternatively an appropriately trained healthcare professional Assistant to procedure

Table 2 Comparison of various routes and techniques of sedation in clinical practice.

Route	Advantages	Disadvantages
Oral	Convenient, easy, inexpensive, relatively safe depending on dose	Cannot titrate drug, delay in onset, higher doses and polypharmacy increases risk, no oral reversal agent
Intravenous or intramuscular	Rapid onset, reliable, consistent, potential for dose titration, reversal agents	Over sedation possible, puncture difficult in needle phobic patients or poor venous access
Inhalation of nitrous oxide	Convenient, easy, consistent, rapid onset, odourless, well tolerated, amnesic	Acceptance of the nasal hood may be difficult, nausea and vomiting, requires scavenging
Music	Convenient, easy, inexpensive, safe	Acceptance, trained assistant in room
Hypnosis and digital sedation	Convenient, easy, inexpensive, safe	Acceptance, trained assistant in room

analgesic drugs to control post-procedural symptoms [24]. These drugs are effective for treating inflammation but have side effects that can potentially affect cardiac, gastrointestinal, and renal systems. Physicians have to make their decision on a case-by-case basis after evaluation of the pain tolerance and anxiety level as well as on the level of discomfort expected during or after the procedure, to meet patient's expectation (Fig. 1). The desired endpoint for sedation and analgesia has to be decided before the procedure, and medications or means should be used incrementally until this endpoint is achieved.

Beyond anesthesiologist-driven sedation or general anesthesia, which are out of the scope of this review, radiologist-controlled sedation involves titrating aliquots of hypnotic drugs such as midazolam. Midazolam is used because of its efficacy, rapid onset of action, and short elimination half-life (1—4 hours). Underdosing and overdosing may occur. According to the Practice Guidelines for Moderate Procedural Sedation and Analgesia [18], combinations of sedative and analgesic agents must be administered as appropriate for the procedure and the condition of the patient. It requires a preoperative thorough evaluation of patients' conditions. Maintaining vascular access throughout the procedure and until the patient is no longer at risk for cardiorespiratory depression is also mandatory. Furthermore, the administration of intravenous sedative/analgesic drugs has to be performed under surveillance in small, incremental doses, or by infusion, titrating to the desired endpoints. Patients must be continuously monitored to assess the depth of sedation and to recognize signs of over-sedation (Table 3). Heart rate, blood pressure, pulse rate and peripheral oxygen saturation must be monitor [25]. All patients receiving moderate sedation should receive supplemental oxygen through nasal prongs or by mask and should have adequate venous access. As monitoring during sedation is the key to a safe practice, it would make the radiologist-controlled sedation relatively

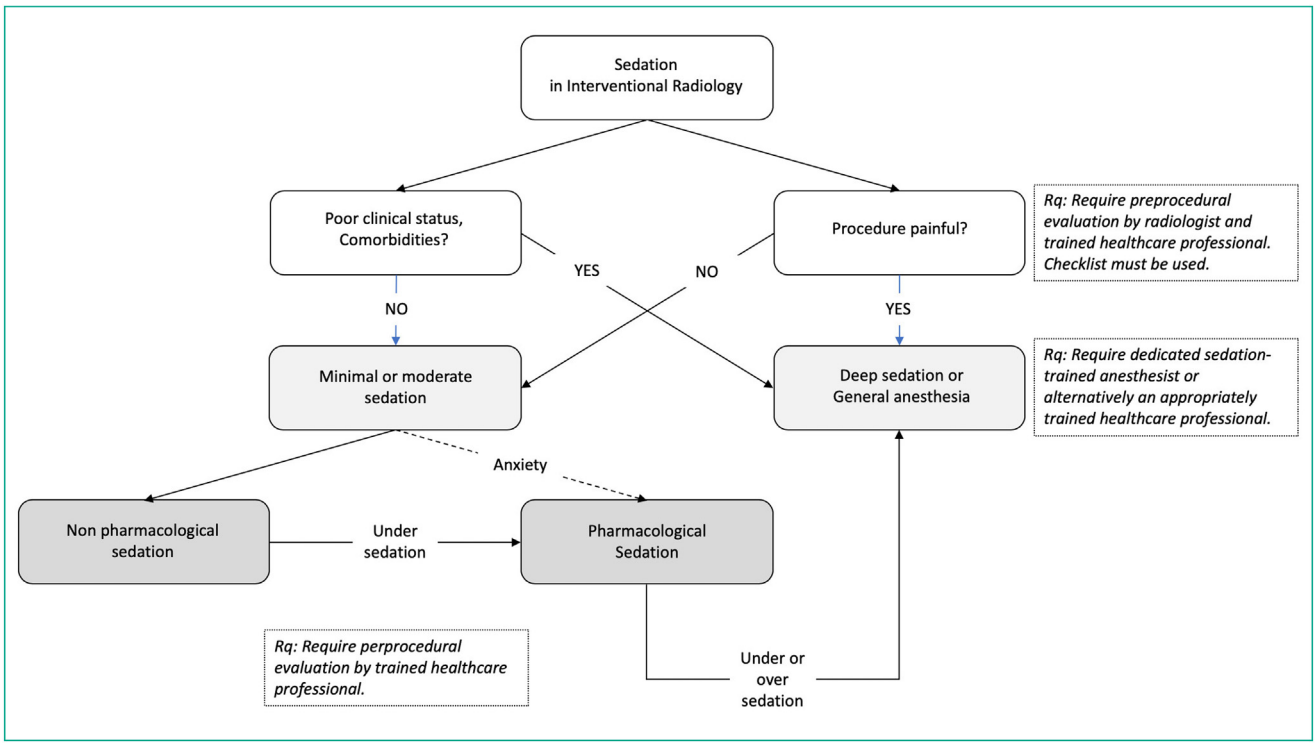

Figure 1. Decision tree for sedation in interventional radiology.

Table 3 Checklist for sedation in interventional radiology.

Assessment	Sedation	Recovery	Outcomes
History and physical examination	Oxygen and suction	Hand over and transition of care performed	Unintended events
Consent obtained and explanation of sedation level given	Monitors on and functioning (pulse oximetry, ECG, blood pressure)	Pain assessment performed	Clinician experience
Nil per os status verified	Necessary team members in attendance (at least 1 physician)	Discharge criteria checked	Patient experience
Patient confirmed as suitable for the level of sedation	Patient re-identified	Oral and written instructions provided, including follow-up instructions	
Recovery and escort plans verified	Procedures confirmed	Escort plan re-verified	
Functional venous access	Allergies confirmed		
Medications (sedation, procedure, rescue)	Open communication demonstrated		
Equipment (sedation, procedure, rescue)			
Under and oversedation backup plan reviewed			

challenging in a daily practice for a small IR team practicing outside the operative rooms without direct access to anesthesiologists. Moreover, recent studies demonstrated that such sedation may be associated with poor functional outcomes and higher mortality in highly technical procedures such as intra-arterial thrombectomy [26]. Furthermore, it seems that sedation does not reduce duration of intervention or procedure-related complications. Such events contribute to worse clinical outcomes and higher costs [27]. The most common adverse effects of drug sedation are

Table 4 Conventional drugs and means available in routine in Interventional Radiology to obtain adequate minimal to moderate sedation and analgesia according to the level of pain expected. A clinical evaluation of the patient before, during and after the procedure is mandatory.

	Before the procedure	Per procedure	24 h post procedure	
Analgesia	Local anesthesia		Lidocaine 20 mg + sodium bicarbonate 8.4% Option: nerve block Ropivicaine 20 mg	
	Analgesia Level 1 (mild pain)	Paracetamol 1 g		Paracetamol 1 g/6 h
	Analgesia Level 2 (medium pain)		Nefopam 20 mg Option: Tramadol 50—100 mg	Nefopam 20 mg/6 h Option: Tramadol 50—100 mg/4 h
	Analgesia Level 3 (severe pain)		Morphine 1—2 mg + bolus 2 mg/5 min (max 10 mg)	Refer to anesthetists
	Non-steroidal anti-inflammatory drug (dose adapted to renal function)		Ketoprofen 100 mg	Ketoprofen 100 mg/12 h
	Other	Odansetron 2 mg	Odansetron 4 mg Omeprazole 20 mg	Odansetron 4 mg/6 h
Sedation	Pharmacologic	Diazepam 5 mg	Titration of midazolam 1 mg Nitrous oxide	
	Non pharmacologic		Music Hypnosis Digital Sedation	

oversedation/apnea (60.2%), hypoxemia (42.2%), and aspiration (24.1%) [28]. The most common unplanned interventions are the use of reversal agents (55.4%) and prolonged bag-mask ventilation (25.3%). The most common minor complications are postoperative nausea and vomiting (1.06%), inadequate pain control (1.01%), and hemodynamic instability (0.62%) [29]. The most common major complications reported were serious hemodynamic instability (0.10%) and upgrade of care (0.10%). Overall mortality is 0.02%. Women are more likely to experience adverse effects than men. Malignancy, cardiovascular comorbidities, long-term opioid therapy or active substance abuse, an age > 65 years, and sleep apnea are associated with increased risks. All these factors are often encountered in patients who undergo IR procedures [29]. Some authors demonstrated the feasibility of patient-controlled analgesia during the procedure using a pump [30] which would be helpful in the context of IR. This allows the patient to self-control their sedation/analgesia during the procedure which may limit the occurrence of adverse events. However, further evaluation is needed.

Nitrous oxide sedation

Nitrous oxide (N_2O) analgesia is safe and effective for use in IR in a wide variety of situations requiring pain and anxiety management [31,32]. N_2O has been used in radiology to control pain and distress in pediatric population. N_2O is an odorless and colorless gas with anxiolytic, analgesic, and amnestic properties, along with rapid onset and recovery, which represent the ideal characteristics of a sedative. However, N_2O alone may not provide a sufficient analgesic effect in procedures that may cause severe pain. N_2O requires patient cooperation as it is important that the patient be reminded to breathe through the nose in order for the gas to work. Moreover, the IR team must control the administration of N_2O (Table 5). The patient should be questioned as to how he is feeling to ensure an optimal administration. If the nitrous level being administered is too low, the patient will not be receiving an effective anxiolytic dose. If the nitrous level is too high, unwanted side-effects may occur (Table 6). The most common adverse effects associated with N_2O are nausea, vomiting and agitation. In addition, stabbing central chest pain, O_2 desaturation, apnea > 15 seconds, stridor, and tonic-clonic seizure have been reported. Moreover, it must be used in well-ventilated rooms to avoid affecting the operator. Therefore, N_2O may be useful for short-duration procedures in cooperating patients adequately screened.

Non-drug sedation

A specific management of anxiety should supplement the analgesia medication in selected patients (Fig. 1, Table 7), especially those with high anxiety scores [33]. The management of patient's anxiety influences the perception of pain. Patient's anxiety is correlated with a relational commitment of professionals. It can basically start with elimination of negative language from the dialogue replaced by positive or neutral language to create self-confidence and relaxation

Table 5 Considerations before nitrous oxide inhalation.

Condition	Consideration
Blockages (eustachian tubes, bowel, acute sinusitis)	Air volume expansion, rapid pressure increase can occur, may result in pain or injury
Nasal obstruction	May interfere with ability to inhale gases, medical consult recommended
Chronic obstructive pulmonary disease	May interfere with hypoxic drive, medical consult recommended
Pneumothorax	Absolute contraindication
Respiratory infections	May interfere with ability to inhale gases, medical consult recommended
Pregnancy	Absolute contraindication during first trimester, medical consult recommended for second and third trimesters
Psychiatric, psychological, personality, compulsive disorders	Unpredictable result, medical consult recommended
Current or history of drug use/addiction	May enhance or potentiate actions
Epilepsy, multiple sclerosis	May trigger if hypoxia is experienced, medical consult recommended
Increased intracranial pressure	Absolute contraindication
Immune-compromised patients	May trigger if hypoxia is experienced, medical consult recommended

Table 6 Signs and symptoms of ideal nitrous oxide sedation.

Lighheadness	Tingling of hands and feet
	Feeling of warmth, flushing of face
	Relaxed body, arms and legs
	Numbness of circumoral region
	Feeling of euphoria
	Feeling lightness or heaviness of body
Oversedation	Irritation or agitated
	Inability to communicate
	Sleepiness or dreaming
	Hallucinations
	Nausea
	Vomiting
	Loss of consciousness

[34]. Relaxation breathing is also helpful. Music and clinical hypnosis has showed more pronounced effects on pain and anxiety reduction [35,36].

Music

The human response to stress may be modulated by auditory input such as music. The factors that add to heightened stress, such as uncomfortable unfamiliar environment, or loss of control, may be attenuated by the distracting and calming effects of music. It has been suggested that pain and auditory pathways inhibit each other. The calming effect of music is potent enough to decrease the sedative and analgesic needs [37]. Music can easily be implemented as adjunctive mean in IR rooms.

Clinical hypnosis

Clinical hypnosis uses to be delivered on a one-on-one basis by a trained nurse, anesthesiologist or radiologist. The principle of these techniques is based on verbal suggestions, particularly on sensory elements, made by the professional, which creates a modified state of consciousness, leading the patient to a dissociative state, thus modifying the perceptions of the pain [14,38—42]. Studies have shown that hypnotic processes modify internal (self-awareness) as well as external (environmental awareness) brain networks similarly as intravenous sedation [14]. Brain mechanisms underlying the modulation of pain perception under hypnotic conditions involve cortical as well as subcortical areas including anterior cingulate and prefrontal cortices, basal ganglia and thalami. Combined with local anesthesia and moderate sedation in patients undergoing procedures, clinical hypnosis is associated with improved peri- and postoperative comfort of patients.

Unfortunately, clinical hypnosis has been poorly evaluated in IR. In a prospective, randomized, single institution study, structured attention and self-hypnotic relaxation proved beneficial during IR procedures [43]. It has been shown to significantly reduce drug requirements during procedures [44,36]. The use of adjunct clinical hypnosis with sedation reduces cost during procedures compare to those with standard intravenous sedation [45]. However, the context of IR complicates the implementation of hypnotic continuous relational support alongside the patient by a radiology professional. Continuous presence of professional in the IR room means exposure to X-rays and thus adequate radiation protection conditions are required [46]. Other obstacles are the difficulties to standardize clinical hypnosis to reduce acute pain associated with medical procedures [47], such as the need for specific training of IR professionals with this type of technique, as well as the heterogeneity of the responses to the hypnotic suggestions of the patients themselves who do not have equivalent thresholds of hypnosability [48,49]. For these reasons, although the training of staff is reported to be relatively simple, the practice of using clinical hypnosis in IR is not yet widespread.

Table 7 Patient selection for non-pharmacologic sedation according to classification of physical status by the American Society of Anesthesiologists.

ASA score	Description	Medical history	Candidate for non-pharmacologic sedation	Required competences
I	Normal, healthy patient	Unremarkable medical history	Excellent	Interventional radiologist
II	Patient with mild systemic disease, no functional limitation	Mild asthma, controlled seizure disorder, anemia, or controlled diabetes mellitus	Good to very good	Trained assistant to monitor patient Assistant to procedure
III	Patient with severe systemic disease or definite functional limitation	Severe asthma, poorly controlled seizure disorder, pneumonia, poorly controlled diabetes mellitus, moderate obesity	Average	Interventional radiologist Dedicated sedation-trained anesthetist or alternatively an
IV	Patient with severe systemic disease that is a constant threat to life	Sepsis, advanced degree of pulmonary, cardiac, hepatic, renal, or endocrine insufficiency	Poor	appropriately trained healthcare professional Assistant to procedure
V	A moribund patient who is not expected to survive without intervention	Septic shock, Severe Trauma	Very poor	
E	Emergent procedure			

From virtual reality to digital sedation

Virtual reality (VR) technology has been studied for its clinical applications [50,51]. VR may be used as a non-pharmacological mean to mitigate acute procedural pain [52—56]. It has been shown to be effective in alleviating the perception of pain, anxiety and general discomfort in adults and children. VR is a digital tool that isolates a patient from the real world and can be useful for reducing pain in medical procedures such as burn care or punctures [57], although the level of evidence from the studies remains low. Eleven randomized studies were found and nine crossover studies [58]. None of these studies concerned directly IR. In the meantime, the majority of the studies put in evidence reduced self-assessment of pain scores in the VR use group with an average effect size, which weights the results of a previous meta-analysis which concluded wide effect size of the use of the VR on reduction of pain [58].

Beyond these existing solutions providing VR as a distracting tool, some studies highlight the possibility of developing ''VR hypnosis'' or ''digital sedation''. Digital sedation consists in using a three-dimensional, immersive and VR technology to guide the patient through the same steps as those used when clinical hypnosis is induced through an interpersonal process [47,59—61] (Fig. 2). Digital sedation sessions can suggest sensations (auditory, visual or even kinesthetic) that patients sometimes have difficulty imagining through verbal suggestions offered by a professional trained in clinical hypnosis. The links between hypnotic process and VR immersion have interesting clinical implications in the context of analgesia and anxiolysis during procedures performed in IR. Indeed, VR can capture the attention of patients undergoing IR procedures. The illusion of entering the computer-generated three-dimensional environment is known as ''presence'' [62]. This concept of presence is considered to be the key factor in making immersive VR more effective at controlling pain than traditional methods of distraction such as video games or television [60]. The feeling of entering the virtual world strengthens the patient's presence in the environment and distracts attention from pain [63]. The neurophysiological mechanisms of VR efficacy on pain perception are not clearly understood [54]. A recently published study compared digital sedation versus midazolam sedation in endoscopic urological surgeries under epidural anesthesia [64]. The results of this study suggest that digital sedation is more effective than midazolam sedation in terms of patient satisfaction and anesthetist satisfaction. Patients in the VR group had fewer respiratory side effects during surgery. Although evidence of the effectiveness of VR distraction to reduce pain and anxiety builds up [58], the analgesic efficacy of this technique is still poorly studied in medical procedures as well as in IR [65]. It would worth to study as immersion in a hypnotic experiment induced by the VR of a patient having to undergo a procedure in IR could saturate his sensoriality, thus reducing the nociceptive perceptions and anxiety correlated with this procedure. Hypnosis in VR could also increase the sense of self-efficacy in managing stress. At the early stage of a disease, this sense might allow the patient to discover that he has the capacity to cope emotionally during anxiety-provoking medical examinations and thus optimize one's own skills to further reduce anxiety by increasing self-efficacy in managing stress.

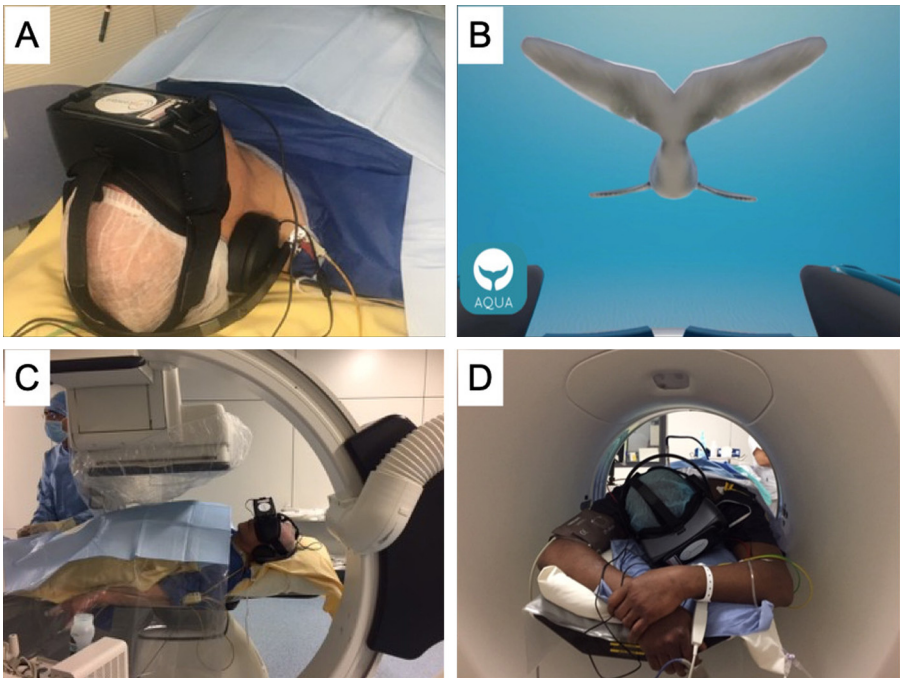

Figure 2. Digital sedation in interventional radiology. A. The device is composed of a virtual reality mask connected to headphones. B. Image of a sedation module projected into the mask (Aqua Module, courtesy of Oncomfort SA). The patient is invited to breath at the same pace as the whale's tail motion. C. Embolization performed under cone beam computed tomography guidance and digital sedation. The skin and deeper tissues over the artery in the groin were anesthetized with local anesthetic. D. Percutaneous computed tomography-guided renal cryoablation performed under local anesthesia and digital sedation. Patient received intravenous anesthetic as well as a paravertebral T10 nerve block. The skin and deeper tissues over the kidney were anesthetised with local anesthetic.

Conclusion

Preliminary results from several studies demonstrated the feasibility, the efficacy and the safety of several sedative techniques in IR. Beyond pharmacological sedation or hypnosis, digital sedation could reduce the anxiety and pain associated with IR procedures and may provide to the patient the adequate tools to optimize their ability to cope with painful and anxiety-provoking situations, in addition to improving post-procedural outcomes. Although limitation to these preliminary results is the small number of patients enrolled in the studies, digital sedation appears anyway as a simple and promising alternative to drug sedation. Further larger evaluation is mandatory before drawing definitive treatment decision tree to guide interventional radiologists.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

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CRediT authorship contribution statement

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Disclosure of interest

The authors declare that they have no competing interest.

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