Pain management during intravitreal injection: integrative review

Manejo da dor durante a injeção intravítrea: revisão integrativa

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ABSTRACT

BACKGROUND AND OBJECTIVES: Intravitreal injection is a very common surgical procedure in the treatment of diabetic retinopathy, diabetic macular edema, and retinal vein occlusion. Because it's a treatment that causes pain and discomfort for the patient, therapies that reduce procedural pain are necessary. The aim of the study was to conduct an integrative review on pain management during administration of intravitreal injection.

CONTENTS: The study was carried out in January 2021 in three databases (Pubmed, Bireme and Scielo) using the descriptors "intravitreal injections", "pain management" and "analgesia". After reading and analysis, 15 articles were selected. The results show several factors associated with pain management during intravitreal injection, such as the use of different anesthetics, needle gauge, injected medication, different surgical instruments and use of music.

CONCLUSION: Studies have shown that proparacaine, especially when associated with subconjunctival lidocaine, ranibizumab and alternative techniques for intravitreal injection are preferable approaches to pain management during the procedure.

Keywords: Analgesia, Intravitreal injections, Pain, Pain management.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A injeção intravítrea é um procedimento cirúrgico muito comum no tratamento de doenças como a retinopatia diabética, o edema macular diabético e a oclusão da veia da retina. Por ser um tratamento que gera dor e desconforto ao paciente, terapias que diminuam a dor procedimental são necessárias. O objetivo deste estudo foi realizar uma revisão integrativa sobre o manejo da dor durante a administração de injeção intravítrea.

CONTEÚDO: Estudo realizado no mês de janeiro de 2021 em três bases de dados (Pubmed, Bireme e Scielo) com o uso dos descritores "injeções intravítreas", "manejo da dor" e "analgesia". Após a leitura e análise, 15 artigos foram selecionados. Os resultados evidenciaram diversos fatores associados ao manejo da dor durante a injeção intravítrea, como o uso de diferentes anestésicos, calibre da agulha, fármaco administrado, diferentes instrumentos cirúrgicos e uso da música.

CONCLUSÃO: Os estudos demonstraram que a proparacaína, principalmente quando associada à lidocaína subconjuntival, o ranibizumabe e as técnicas alternativas de aplicação da injeção intravítrea são abordagens preferíveis no manejo da dor durante o procedimento.

Descritores: Analgesia, Dor, Injeções intravítreas, Manejo da dor.

INTRODUCTION

Intravitreal injection (IVI) is considered one of the greatest advances in techniques for the treatment of retinal diseases. This procedure involves the application of antiangiogenic drugs or steroids in the vitreous, the internal and posterior extension of the eye[1].

IVI are effective in diseases such as diabetic retinopathy, diabetic macular edema and retinal vein occlusion[2]. Despite being effective, the treatment also provides an uncomfortable and painful experience, which may result in non-adherence of patients in cases of diseases that require continuous treatment, negatively impacting the intended outcome.

Although it's a minimally invasive procedure, performed with topical anesthetics, pain and discomfort are frequent in the patient's experience[2]. Thus, professionals have sought scientific evidence to support their practice and promote an adequate pain management for their patients.

Since pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[3], unpleasant sensations such as fear, insecurity and anxiety are often associated with the painful phe-

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nomenon, especially in nociceptive diagnostic and therapeutic procedures[3,4], such as IVI.

Although there are studies on the intensity of pain caused by IVI and its related factors, the available literature on its management is still scarce.

Therefore, the objective of this study was to perform an integrative review on the management of pain related to IVI.

CONTENTS

An integrative review that sought to answer the following guiding questions: what are the factors associate to pain related to IVI? What are the pharmacological and non-pharmacological methods used in its management?

The Whittemore methodological reference steps were adopted: problem identification, search, data base assessment, analysis, and presentation of results[5].

During January 2021, two independent reviewers performed systematic searches on the Pubmed, Virtual Health Library, and Scielo databases using the following DeCS/MeSH controlled descriptors in English, Portuguese, and Spanish: intravitreal injections (injeções intravítreas, inyección intravítrea), pain management (manejo da dor, manejo del dolor) and analgesia, united by the Boolean operators AND and OR.

Studies included were original primary; published between 2011 and 2021; with full text available in English, Portuguese and Spanish languages; investigating the evaluation and management of pain related to IVI in adult patients. Studies using animal models, systematic, integrative, narrative and scoping reviews, editorials, letters to the editor, commentaries, experience reports and research involving pediatric populations were excluded.

Duplicate manuscripts were counted only once, and then studies were screened based on their titles and abstracts. Studies considered relevant were read in full and selected according to the eligibility criteria. Disagreements were resolved by consensus or by a third reviewer (Figure 1).

After the selection stage, the reviewers extracted the data from the articles in a standardized spreadsheet and evaluated the level of evidence using the Oxford Center for Evidence-Based Medicine 2011 (OCEBM) tool, which classifies the articles into five levels of evidence (1 to 5) according to the type of research question and study design. The level of evidence can be lowered according to study quality, imprecision, incompatibility between type of question and design, inconsistency between studies, or because the absolute effect size is too small. On the other hand, the level can be raised if a large or very large effect size is observed[6].

The characteristics of the studies included in the final analysis are shown in table 1. During the synthesis of qualitative data, three thematic categories emerged: associated factors, pharmacological management and non-pharmacological management of pain related to IVI. All studies were published between 2014 and 2020, but most were published in the last five years (73.3%) and from research conducted in the Asian continent (66.7%).

Of the articles selected for review, eight (53.3%) were classified as 1B (randomized clinical trial - RCT), four (26.7%) as 3B (case-control study), and three (20%) in the 2B category (cohort study or clinical trial of lower quality), according to the evidence levels of the OCEBM tool.

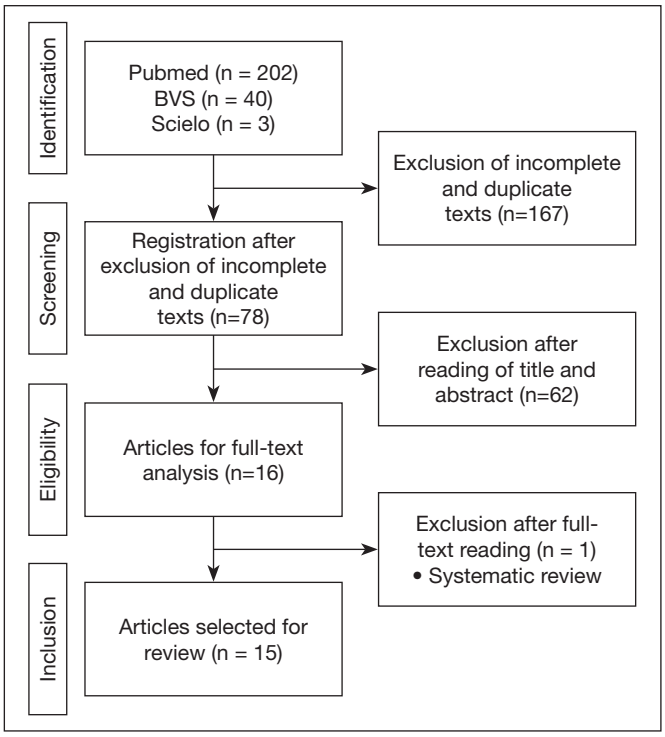

Figure 1. Flowchart of identification and selection of articles

Although most studies are RCT, only two recruited more than 1.000 patients. This demonstrates the need for conducting RCT with larger sample sizes and sufficient statistical power to recommend different approaches of pain relief during IVI. This concern is even more evident in investigations on non-pharmacological management, as only one RCT with a small sample size was found.

The main results of the studies included in this review are presented in table 2.

Factors associated with pain related to the intravitreal injection

Despite its clinical relevance, pain is still neglected and undervalued, especially procedural pain. Several diagnostic and therapeutic procedures are potentially painful, but few services have analgesia protocols. Ophthalmologic procedures, such as IVI, are usually performed only with the use of local anesthetic eye drops. In the present review, it was possible to identify some factors associated with procedural pain related to IVI such as needle size, for example. There is a tendency to use smaller needles, because it's considered that they require less force to be used. Three clinical trials have compared pain intensity with the use of 27-G and 30-G needles. However, no significant differences in pain scores were observed[8,9,11].

The site of IVI application was also investigated, revealing lower pain scores when the procedure was performed in the superior nasal quadrant and higher in the superior temporal quadrant[14]. Additionally, this clinical trial demonstrated an inverse relationship between anesthetic concentration and pain score. Therefore, IVI administered at sites of higher concentration resulted in lower pain intensity.

Table 1. Description of studies included in the review

Autores	Country of origin	Design and level of evidence	Sample size	Objective
Moisseiev et al.[7]	Israel	Non-randomized, intervention study 2B	57 patients	Assess the pain associated with Ozurdex IVI and compare it to that associated with bevacizumab IVI.
Güler et al.[8]	Turkey	Non-randomized, intervention study 2B	70 patients	Compare patients' pain scores during IVI with 27-G bevacizumab needles and 30-G ranibizumab needles.
Haas et al.[9]	Austria	Randomized, blind, clinical trial 1B	280 patients	Evaluate the influence of the needle size used for IVI on the patients' experience of pain.
Alattas[10]	Saudi Arabia	Prospective observational study 3B	56 patients	Compare patients' acceptance and correlate their pain level for bimanual versus metal speculum fixation in IVI.
Loureiro et al.[11]	Portugal	Cross-sectional, randomized study 3B	54 eyes	Assess the impact of needle size on intraocular pressure and pain: compare the effect of 30-gauge versus 27-G needle size on patients' intraocular pressure and pain experience after bevacizumab IVI.
Shin, Park and Kim[12]	Korea	Prospective observational study 3B	147 patients	Investigate factors associated with pain intensity after IVI and factors that may be associated with changes in pain intensity in patients who received repeated injections.
Bilgin and Bilak[13]	Turkey	Non-randomized, intervention study. 2B	72 patients	Compare patients' pain scores during ranibizumab and aflibercept IVI based on patient feedback.
Karimi et al.[14]	Iran	Randomized clinical trial 1B	1.004 patients	Assess the relation between site of injection and level of pain after bevacizumab IVI.
Khaqan et al.[15]	Pakistan	Randomized study 1B	2.250 patients	Compare the level of discomfort caused between a customized disposable kit and a conventional stainless-steel instrument
Soh et al.[16]	Singapore	Randomized, prospective study 1B	140 patients	Evaluate the clinical performance of the assistant device of IVI (InVitria) compared to the conventional free hand technique.
Blyth et al.[17]	England	Prospective observational study 3B	58 patients	Compare the use of the conventional IVI method with the InVitria device.
Raevis et al.[18]	United States	Randomized, open clinical trial 1B	99 patients	Test discomfort experienced during IVI with eyelid retraction with eyelid speculum, cotton-tipped applicator (CTA) and unimanual eyelid retraction techniques.
Örnek et al.[19]	Turkey	Randomized, prospective study 1B	96 patients	Compare the anesthetic efficacy of topical levobupivacaine 0.75% and proparacaine 0.5% in patients undergoing IVI.
Andrade and Carvalho[20]	Brazil	Randomized, prospective study 1B	92 patients	Compare the anesthetic efficacy of topical proparacaine drops, subconjunctival lidocaine and lidocaine gel 2%.
Chan et al.[22]	Hong Kong	Randomized, parallel, controlled clinical trial 1B	76 patients	Assess the effect of music during IVI.

Table 2. Results of analyzed studies

Authors	Results
Moisseiev et al.[7]	During the IVI, there were no significant differences between the scores of pains when Ozurdex and bevacizumab were used. The score of pain was higher in pseudophakic eyes (VAS=32.23 ± 23.0; p=0.005) when compared to phacic eye (VAS=15.6 ± 16.8).
Güler et al.[8]	Ranibizumab showed less influence on pain (VAS=1.06 ± 0.91) compared to bevacizumab (VAS=1.94 ± 1.55; p=0.005). Women experienced more pain with bevacizumab injection (VAS=2.35 ± 1.77) than with ranibizumab injection (VAS=1.16 ± 1.01; p=0.016).
Haas et al.[9]	No association between needle gauge and pain intensity was found, and the suggested approach is according to the patient's need. Pain perception was more significant in older patients and women.
Alattas[10]	The use of bimanual fixation provided the patient with more comfort and less pain (0.53 ± 0.62) than the use of metal fixation (1.91 ± 1.14; p=0.003).
Loureiro et al.[11]	There was no significant difference in pain scores between the 27-gauge (VAS=3.0 ± 2.5) and 30-gauge (VAS=3.2 ± 2.6; p=0.003) needles.

Continue...

Table 2. Results of analyzed studies – continuation

Authors	Results
Shin, Park and Kim[12]	Women (VAS=3.1 ± 1.5) were more susceptible to pain than men (VAS=2.4 ± 1.2; p=0.003). The anterior chamber paracentesis procedure reduced pain during the procedure, as well as the anti-VEGF IVI showed lower pain scores. Patients who received repeated injections noted pain perception less or similar to previous procedures.
Bilgin e Burak[13]	Application of ranibizumab (VAS=3.28 ± 2.45; p=0.04) showed lower pain intensity than aflibercept (VAS=4.20 ± 2.30). Women in both groups experienced more pain (VAS=4.83 ± 2.67; p=0.001) during the procedure than men (2.87 ± 1.81). Additionally, pain among women was even higher with aflibercept injection (VAS=5.20 ± 2.59).
Karimi et al.[14]	The following pain scores were observed according to the quadrants of application: superior nasal (1.5 ± 1.7), inferior nasal (3.0 ± 2.3), superior temporal (4.0 ± 2.0) and inferior temporal (3.0 ± 2.1). A statistically significant correlation was found between patient sex and pain score (p<0.001).
Khaqan et al.[15]	The use of the disposable kit is more beneficial for painless tissue handling, as well as being faster and less costly. Of 1.500 eyes submitted to the use of the kit, no pain was reported by patients in 1.231 eyes (82.06%), while with the conventional method no pain was perceived in 1.014 of the 1.200 analyzed eyes (84.5%).
Soh et al.[16]	The pain scores did not present significant differences, and in the conventional technique of IVI the VAS was equal to 2.03 ± 1.73, while in the InVitria technique, the VAS was 2.13 ± 2.20. However, it was found that the new technique has a shorter execution time than the conventional one.
Blyth et al.[17]	When applying the questionnaire, the data collected showed an improvement in pain scores in each phase of the procedure in cases where InVitria was used compared to the conventional method; as for the time spent in application, InVitria was, on average, 1 minute and 32 seconds faster than the conventional method.
Raevis et al.[18]	The palpebral retraction was less painful with the unimanual and CTA techniques, providing more comfort to the patient. Pain scores for eyelid retraction: unimanual group (0.778 ± 0.70); CTA group (0.945 ± 1.28); speculum group (1.561 ± 1.28) significant difference between groups (p=0.006).
Pharmacological management of IVI-related pain	
Örnek et al.[19]	Anesthesia with proparacaine (VAS=34.18 ± 14.83) is more effective in relieving pain during IVI than levobupivacaine (VAS=44.77 ± 16.42; p=0.003).
Andrade and Carvalho[20]	Subconjunctival lidocaine 1% associated with proparacaine is more effective in reducing pain scores than proparacaine 0.5% and lidocaine gel 2%.
Non-pharmacological management of IVI-related pain	
Chan et al.[22]	There were no significant differences between the pain scores of the music therapy and control groups (VAS=31.92 ± 28.30 vs. 34.95 ± 30.49, respectively, p=0.655). Nevertheless, patients in the experimental group reported less anxiety, and also preferred the use of music in upcoming procedures.

VAS=visual analog scale.

Some devices used in the conventional technique of IVI caused discomfort the patient, among those, the meta speculum is considered the most painful[10,15]. To reduce pain caused by this instrument, three studies tested different techniques for palpebral retraction, such as the use of a disposable kit, unimanual method, bimanual method, and with the cotton-tipped applicator. In all cases, the experimental technique was associated with lower pain scores when compared to the conventional technique[10,15,18].

There are also devices such as the InVitria (FCI Ophtalmics, Pembroke, MA, USA), made of recyclable and disposable plastic, responsible for keeping the eye open and fixing it in place, also adding an anesthetic effect. They help in the application of IVI, promoting greater safety for the patient and precision for the surgeon, as well as shorter duration of the procedure. When compared to the conventional method, this device has generated results that benefit its use. Two studies concluded that despite the similarity in pain scores between the two methods, InVitria has a shorter application time, contributing to the comfort of the patient[16,17].

The association between pain and the type of anti VEGF substances acting on the endothelial growth factor administered was evaluated in two studies. It was found that the application of ranibizumab was associated with a lower pain score and report of good experience when compared to aflibercept and bevacizumab[8,13]. However, when compared to Ozurdex, the latter did not show a significant difference[7].

Although repeated IVI administrations may contribute to non-adherence of patients, one of the studies revealed that pain perception diminishes over the course of treatment[14.] Other factors such as age, sex, and diseases associated with retinopathy have been investigated. Some research suggested that elderly patients are more sensitive to pain[7,9] while others found no significant relation between pain and age[12]. As for sex, women reported higher pain intensity than men[8,9,12-14]. The presence of comorbidities was associated with higher pain scores[7].

Pharmacological management of pain related to intravitreal injection

Despite being widely used in the application of IVI, there is no consensus about which local anesthetic is more effective for pain relief during the procedure. Among the selected studies, two investigated the analgesic efficacy of levobupivacaine, proparacaine, and lidocaine[19,20].

Levobupivacaine, a bupivacaine isomer, is one of the most used substances in IVI clinical practice due to its lower neurotoxicity. Despite it's effectiveness, patients in the experimental group reported higher pain scores, and proparacaine 0.5% was the anes-

thetic that presented the best analgesic efficacy[19]. This efficacy increases when proparacaine is associated with subconjunctival lidocaine 1%[20].

Non-pharmacological management of pain relate to intravitreal injection

Non-pharmacological therapies have been gaining more space in health care processes, especially in the *Sistema Único de Saúde* (SUS, Brazil's public health system)[21], due to their low cost, easy use, and low frequency of side effects. Moreover, multimodal pain treatment is a practice that allows the integration of different approaches.

However, studies on this subject are still scarce in ophthalmology. Only one study was included in this category, in which 76 patients were randomized into two groups: control group and music. During the entire procedure, the same music was played for the experimental group, while the control group received conventional treatment[22]. Although there was no significant difference between groups, the patients in the experimental group reported that the experience with music was more pleasant and preferable.

CONCLUSION

Results revealed that the management of pain related to IVI is still underestimated. As for associated factors, alternative techniques of IVI application generated less pain than the conventional one. Furthermore, inconclusive results were found when analyzing the association between pain, sex, age, and needle gauge. Regarding pharmacological methods, it was evidenced that ranibizumab injection resulted in lower pain scores when compared to other anti-VEGFs. The association between 0.5% proparacaine and 1% subconjunctival lidocaine was more effective than other anesthetic eye drops. Studies investigating multimodal treatment, especially non-pharmacological pain management during IVI, are still scarce. Only one study tested the analgesic efficacy of music during IVI, but there were no significant results. Thus, it's important to emphasize the need for additional studies of greater methodological rigor, with samples that provide higher statistical power, in order to know the main factors associated with procedural pain in IVI and test new strategies for its relief.

AUTHOR'S CONTRIBUTIONS

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Data Collection, Conceptualization, Project Management, Research, Methodology, Writing – Preparation of the original, Writing – Review and Editing, Visualization
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Data Collection, Conceptualization, Research, Methodology, Writing – Preparation of the original, Writing – Review and Editing, Visualization
Moniery da Silva Santos
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Conceptualization, Methodology, Writing – Preparation of the original, Writing – Review and Editing, Supervision
Maria do Carmo de Oliveira Ribeiro
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