Effect of Needle Gauge Size on Pain During Intravitreal Anti-VEGF Injection

A Systematic Review and Network Meta-Analysis

Butler, Emilie T.S.; Bjerager, Jakob; Eriksen, Nathalie S.; Hajari, Javad N.; Schneider, Miklos; Faber, Carsten; Subhi, Yousif

Published in:
Ophthalmology and Therapy

DOI:
10.1007/s40123-023-00879-7

Publication date:
2024

Document version:
Final published version

Ophthalmol Ther (2024) 13:801–817
https://doi.org/10.1007/s40123-023-00879-7

ORIGINAL RESEARCH

Effect of Needle Gauge Size on Pain During Intravitreal Anti-VEGF Injection: A Systematic Review and Network Meta-Analysis

Emilie T. S. Butler · Jakob Bjerager · Nathalie S. Eriksen · Javad N. Hajari · Miklos Schneider · Carsten Faber · Yousif Subhi

Received: November 16, 2023 / Accepted: December 20, 2023 / Published online: January 24, 2024

ABSTRACT

Introduction: Concerns related to pain from intravitreal injections are one of the key factors mentioned by patients when asked about therapy. In this systematic review and network meta-analysis, we evaluate the literature of comparative clinical trials on the relationship between needle gauge size and pain experience during intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy.

Methods: We searched 12 literature databases on 14 October 2023 for comparative studies of gauge sizes for intravitreal anti-VEGF injections. The primary outcome of interest was the reported pain experience immediately after the injection. All outcomes of pain were transformed into standardized effect sizes using Cohen's *d*. Using a network meta-analysis approach, we were able to compare all gauge sizes and rank them according to the reported pain experience.

Results: We identified nine eligible studies with data on a total of 998 patients and 1004 eyes. Needle sizes studied were 26-gauge, 27-gauge, 29-gauge, 30-gauge, 32-gauge, 33-gauge, and 34-gauge. A complete network was present, which allowed for a network meta-analysis. We used the thickest (26-gauge) needle as the reference group and observed a clear trend of lower pain experience with thinner gauge sizes (*d*: −0.4, *d*: −2.7, *d*: −3.8, *d*: −4.8, *d*: −4.5, and *d*: −5.3; respectively, for 27-gauge, 29-gauge, 30-gauge, 32-gauge, 33-gauge, and 34-gauge).

Conclusion: A gauge size of 30 or thinner may minimize patient discomfort related to intravitreal anti-VEGF therapy.

Keywords: Intravitreal injection; Anti-VEGF; Pain; Systematic review; Network meta-analysis

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40123-023-00879-7.

E. T. S. Butler · J. Bjerager · J. N. Hajari · M. Schneider · C. Faber · Y. Subhi (✉)
Department of Ophthalmology, Rigshospitalet, Glostrup, Denmark
e-mail: ysubhi@gmail.com

N. S. Eriksen · Y. Subhi
Department of Ophthalmology, Zealand University Hospital, Roskilde, Denmark

J. N. Hajari · C. Faber
Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

M. Schneider
Department of Ophthalmology, Semmelweis University, Budapest, Hungary

Y. Subhi
Department of Clinical Research, University of Southern Denmark, J.B. Winsløws Vej 19.3, 5000 Odense C, Denmark

Key Summary Points

Why carry out the study?

Studies find that patients report a certain degree of fear and anxiety regarding intravitreal injection, and concerns related to pain from intravitreal injections are one of the key factors mentioned by patients when asked about therapy.

We systematically review comparative studies on the needle gauge size used for intravitreal anti-vascular endothelial growth factor injection therapy and the pain experience reported by the patients.

What was learned from the study?

Our network meta-analysis found a clear relationship between thinner needle gauge sizes and lower pain experience from intravitreal injections.

However, pain is a complex experience, and studies report many influencing aspects related to intravitreal injections. Nevertheless, we recommend using the thinnest feasible gauge size when delivering intravitreal injection therapy.

INTRODUCTION

The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has dramatically improved the prognosis of exudative maculopathy [1, 2]. In the USA alone, it is estimated that 5.9 million intravitreal injections were performed in 2016 [3]. The number of intravitreal anti-VEGF injections is growing. Jørstad et al. from Norway reported a 100-fold increase in the number of annual intravitreal anti-VEGF injections from 2006 to 2018 [4], and Thinggaard et al. estimate that the number of annual intravitreal anti-VEGF injections will increase by 50% in Denmark within 5 years [5]. Considering these large figures, it makes great sense to focus on optimizing the procedure to create an efficient, safe, and welcoming service that delivers as painless an intravitreal injection as possible.

Studies find that patients report a certain degree of fear and anxiety regarding the intravitreal injection [6–9], and development of anxiety due to the expectation of pain from the injections [10]. Patients even report sleep disturbance as a result [11], and concerns related to pain from intravitreal injections are one of the key factors mentioned by patients when asked about therapy [12–14]. Although most patients remain in therapy despite these challenges, a minority opt out of treatment due to the burden from repeated intravitreal injections [15]. Hence, guidelines for intravitreal injections often focus on approaches to limit the associated experience of pain [16–18].

One aspect regarding the pain experience is the gauge size of the needle used for intravitreal anti-VEGF injection therapy [16]. In this systematic review, we evaluated the pain experience in relation to gauge size in intravitreal anti-VEGF therapy to provide an overview of the evidence in this field. Further, we used network meta-analysis as a method to compare pain reports across studies and ranked gauge sizes according to pain severity.

METHODS

Study Design

This study was a systematic review and network meta-analysis designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19]. Recommendations of the Cochrane Handbook were followed for practical and analytical guidance [20]. The study protocol was registered in the PROSPERO database (ID: CRD42023474162). This study is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Study Eligibility Criteria and Outcome of Interest

We employed the following eligibility criteria when considering studies for this review:

Population

Patients undergoing intravitreal anti-VEGF therapy with intravitreal injections were included. We did not enforce any criteria on the decision for intravitreal anti-VEGF therapy. No restrictions were made on patient characteristics (e.g., age, sex, race) or any eye characteristics (e.g., phakic/pseudophakic, underlying disease, visual acuity). We did not enforce any restrictions on the anti-VEGF drug employed for such a study; however, intravitreal anti-VEGF therapy considered outside the definition of routine intravitreal anti-VEGF therapy was not eligible for this study (e.g., port delivery devices, experimental delivery systems, implant-based systems). Intravitreal therapy without any anti-VEGF or a combination of anti-VEGF with any other drug category (e.g., antibiotics or corticosteroids) was not considered eligible for this study. We did not enforce any restrictions on the protocol for topical anesthesia but noted such details for the qualitative review.

Intervention and Comparison

Intravitreal injection using any gauge size. Comparison groups were defined as other gauge sizes. Studies without any data on a comparison group were not considered eligible.

Outcomes

Our outcome of interest was the pain experience. We did not apply restrictions on the measure used to report on pain experience. We required that pain was reported by the patient (i.e., not a bystander or the injection provider) and that pain was measured immediately after the injection procedure.

Study Type

We only considered comparative controlled trials. We did not enforce any restrictions based on blinding strategy, randomization, or any other methodological characteristics. We only considered peer-reviewed studies reported in the English language. We did not consider conference abstracts or non-peer-reviewed studies. We did not restrict eligibility based on geography or journal.

Information Source, Search Strategy, and Study Selection

We searched 12 literature databases on 14 October 2023: PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science Core Collection, BIOSIS Previews, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI–Korean Journal Database, Preprint Citation Index, ProQuest™ Dissertations & Theses Citation Index, and SciELO Citation Index. All searches were conducted by one trained investigator (author Yousif Subhi) using search phrases specifically tailored to the individual databases (details are available in Supplementary Material).

Records extracted from the literature search were imported to EndNote X9.3.1. for Mac (Clarivate Analytics, Philadelphia, PA, USA). All records were screened by one author (Yousif Subhi) to remove duplicates and those obviously irrelevant. The remaining records were retrieved for full-text evaluation of eligibility by two authors working independently (Emilie T.S. Butler and Jakob Bjerager). Reference lists were checked for any eligible records not identified by the literature search. The authors then discussed study selection and eligibility with a third author (Yousif Subhi), who provided a final decision if consensus could not be reached.

Data Items, Data Collection, and Risk of Bias within Studies

From each eligible study, we extracted data on study design, study characteristics, study population, intervention/comparisons, and outcomes. Risk of bias within studies was evaluated using the Cochrane risk-of-bias tool version 2 [21]. Two authors worked independently to extract data from studies (Emilie T.S. Butler and Nathalie S. Eriksen) and to evaluate the risk of bias within studies (Emilie T.S. Butler and Jakob

Bjerager). The authors then discussed the data extraction and risk-of-bias evaluation with a third author (Yousif Subhi), who provided a final decision if consensus could not be reached.

Data Synthesis and Risk of Bias across Studies

All studies were reviewed qualitatively in text and in tables. For the quantitative analyses, i.e., the network meta-analyses, we constructed network plots to illustrate the network of direct comparisons and to confirm the existence of a complete network necessary for the analyses. We then used the generalized pairwise modeling approach, which is based on the repeated application of adjusted indirect comparisons [22]. The generalized pairwise modeling approach has been shown to deliver robust results and is comparable to the Bayesian approach and the multivariate modeling approach [22]. All meta-analyses were conducted using MetaXL 5.3 (EpiGear International, Sunrise Beach, QLD, Australia) for Microsoft Excel (Microsoft, Redmond, WA, USA), which uses the generalized pairwise modeling framework. All outcomes of pain were transformed into standardized effect sizes using Cohen's *d*, which is calculated using the ratio of the mean difference between the groups and the standard deviation for the data. The random-effects model was employed to account for potential heterogeneity across studies. Summary estimates were given using 95% confidence intervals (95% CI). Statistical significance was defined as *P* values less than 0.05.

RESULTS

Study Selection

The literature search identified 1809 records. One record known to us was added to the pool of references. From a total of 1810 records, we removed 396 duplicates and 1402 obviously irrelevant records. The remaining 12 records were retrieved in full text for further evaluation of eligibility. No additional records were identified by reviewing reference lists. We found nine studies to be eligible for both the qualitative and the quantitative review (Fig. 1).

Characteristics of the Eligible Studies

Studies collectively summarized data on a total of 998 patients and 1004 eyes [23–31]. Data were reported from participants in Europe (4 studies), Asia (2 studies), North America (2 studies), and South America (1 study). Where reported, eyes were treated for a variety of retinal diseases, most commonly age-related macular degeneration, diabetic macular edema, and retinal vein occlusion. Treatments were performed using bevacizumab [26–29, 31], ranibizumab [23–26, 30], or aflibercept [23, 25, 30]. Pain experience was evaluated using a 10-point numeric rating scale, a 10-point visual analogue scale (VAS), a 5-point Likert scale, and the Wong-Baker FACES scale. These aspects of pain were measured immediately after the injection in all studies, and one study also measured pain later during the day and the following day [25]. The intravitreal injection protocols differed across studies in terms of pre-injection preparation protocol and injection site. Injections were given by physicians or surgeons. Further study characteristics and details of injection protocols are summarized in Table 1.

Needle sizes in studies included 26-gauge (1 study), 27-gauge (4 studies), 29-gauge (1 study), 30-gauge (all 9 studies), 32-gauge (1 study), 33-gauge (3 studies), and 34-gauge (1 study). Seven studies reported patient demographics, and these studies reported a mean age of 60–-78 years and a balanced distribution of male and female sex. Further details of the study groups are summarized in Table 2.

Results of Individual Studies

Güler et al. [26], Haas et al. [27], and Lourerio et al. [28] compared the pain experience of treatment with 27-gauge and 30-gauge needles. Güler et al. found that the thinner 30-gauge needle was associated with lower pain scores, but that the difference in pain experience between the gauge sizes was age-dependent, as

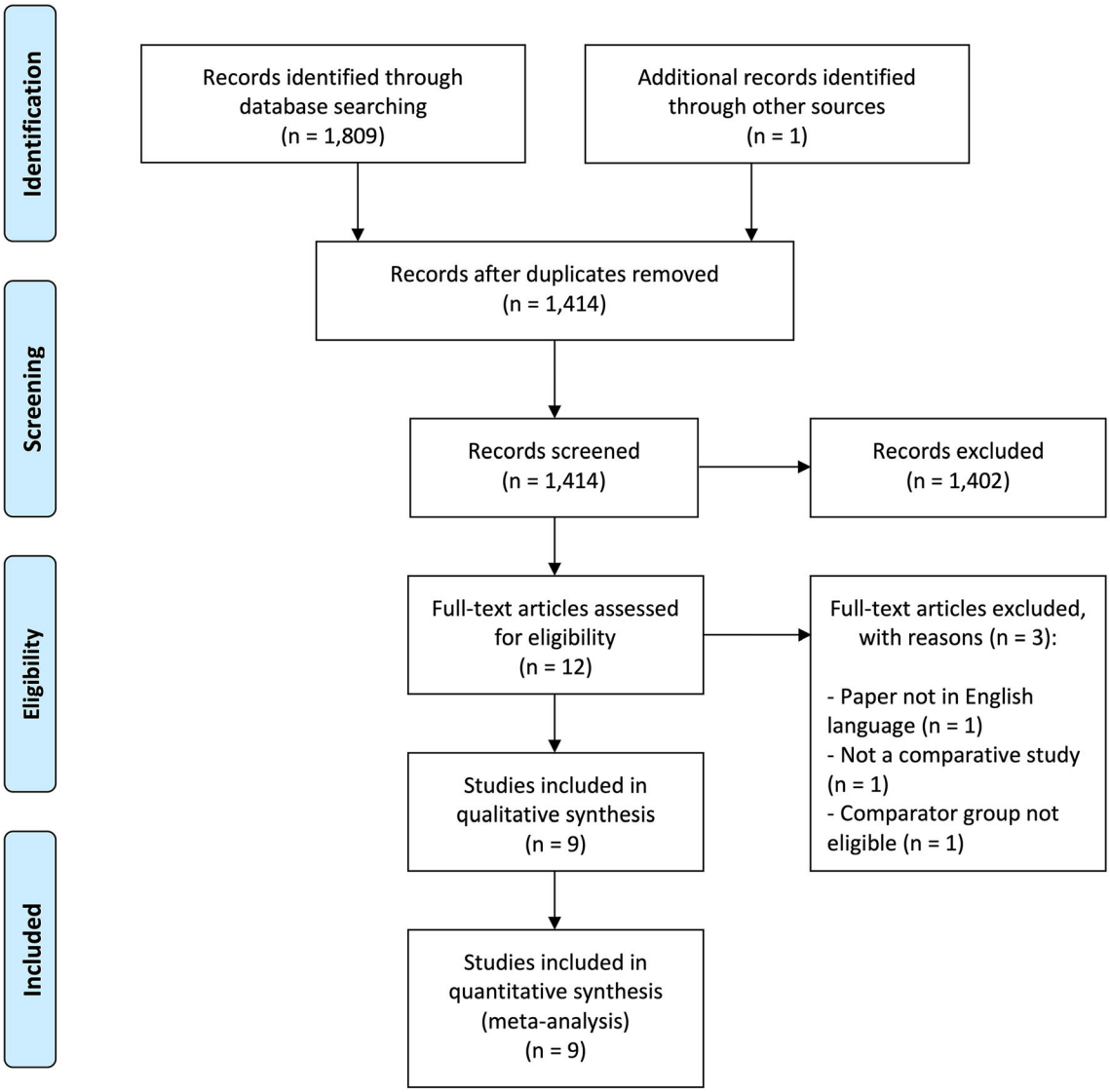

Fig. 1 PRISMA flow diagram of study selection

it was only observed in patients aged < 65 years [26]. Haas et al. found no difference in the pain experience between the two gauge size groups, but reported that the pain experience was positively correlated with higher age, female sex, and number of previous injections [27]. Lourerio et al. found no difference in the pain experience between the two gauge size groups and found no correlation between the pain experience and patient demographics or previous number of injections [28].

Rodrigues et al. compared six types of needles among four needle calibers: 26-, 27-, 29-, and 30-gauge needles [29]. This study found that patients treated with 26-gauge or 27-gauge needles experienced significantly more pain than those treated with 29-gauge or 30-gauge needles [29]. No correlation was found between pain experience and needle length, patient demographics, injection technique, or the temporary intraocular pressure increase after the injection [29].

Table 1 Study characteristics

Reference	Country	Design	Participant eligibility	Details of the anti-VEGF treatment	Pain measurement
Aderman et al. (2018)	USA	Prospective single-center RCT	Patients with AMD, diabetic macular edema, or retinal vein occlusion receiving bilateral anti-VEGF treatment were recruited to participate in this study	- Eye was cleaned with povidone-iodine - Proparacaine was instilled twice approximately 15 s apart - No eye speculum, eyelids were kept apart bimanually, and povidone-iodine was instilled - Intravitreal ranibizumab (0.5 mg/0.05 mL) or aflibercept (2 mg/0.05 mL) was administered 4 mm from the limbus in the inferotemporal quadrant - Injections were performed by physicians - All patients had one eye treated with a 30-gauge needle and the other eye treated with a 33-gauge needle. Allocation of the left or right eye to the needle groups was randomized	Pain was measured with the Numeric Pain Rating Scale, which is a segmented numeric version of the VAS. Pain was measured before and immediately after the injection
Alshahrani et al. (2021)	Saudi Arabia	Prospective single-center RCT	Patients with macular edema due to diabetic retinopathy, exudative AMD, or retinal vasculopathy. Patients were treatment-naïve and the anti-VEGF injection in the study was their first injection. Patients were not included if they had previously experienced a painful ocular condition	- Eye was cleaned with povidone-iodine - Xylocaine gel was instilled; after 10 min, an eye speculum was inserted, and povidone-iodine was instilled - Intravitreal ranibizumab (0.5 mg/0.05 mL) was administered 3.5 mm from the limbus in the inferotemporal quadrant - Injections were performed by retina specialists - Patients were randomized to either 30-gauge or 32-gauge needles	Pain was measured with a VAS from 1 to 10. Pain was measured immediately after the intravitreal injection

Table 1 continued

Reference	Country	Design	Participant eligibility	Details of the anti-VEGF treatment	Pain measurement
Eaton et al. (2013)	USA	Prospective single-center RCT	Patients receiving bilateral anti-VEGF treatment were recruited to participate in this study	- Eye was cleaned with povidone-iodine - Anesthesia was performed with one of three topical methods: subconjunctival lidocaine 2% with epinephrine (81% of participants), topical lidocaine gel 2% (3% of participants), or topical tetracaine 0.5% (16% of participants) - An eye speculum was inserted, and povidone-iodine was instilled again - Intravitreal ranibizumab (0.5 mg/0.05 mL) or aflibercept (2 mg/0.05 mL) was administered - Injections were performed by physicians using methods with which they were most comfortable - All patients had one eye treated with a 30-gauge needle, and the other eye treated with a 33-gauge needle. Allocation of the left or right eye to the needle groups was randomized	Pain was measured on a 5-point Likert scale during the injection, immediately after the intravitreal injection, later that day, and the next day
Güler et al. (2015)	Turkey	Prospective single-center non-randomized comparative trial	Patients were treatment-naïve and the anti-VEGF injection in the study was their first injection. Patients were excluded if previous eye surgery other than for cataract, or a history of herpetic eye disease, glaucoma, uveitis, or active conjunctivitis, keratitis, bullous keratopathy, or use of systemic analgesics or sedatives	- Eye was cleaned with povidone-iodine - Proparacaine 0.5% was instilled, eye speculum was inserted, povidone-iodine was instilled, and proparacaine 0.5% was instilled again - Intravitreal bevacizumab or ranibizumab was administered 3.5–4.0 mm from the limbus in the inferotemporal quadrant - Patients were allocated to either 27-gauge bevacizumab (1.25 mg/0.05 mL) or 30-gauge ranibizumab (0.5 mg/0.05 mL)	Pain was measured on a VAS from 0 to 10. Pain was measured immediately after the intravitreal injection

Table 1 continued

Reference	Country	Design	Participant eligibility	Details of the anti-VEGF treatment	Pain measurement
Haas et al. (2016)	Austria	Prospective single-center RCT	Patients receiving intravitreal injection therapy, ability to report pain perception, and no history of ocular pain related to intravitreal injections, active ocular infection or inflammation, known trigeminal neuralgia, or allergy to drugs involved	- Eye was cleaned with povidone-iodine - Tetracaine 0.5% was instilled, eye speculum was inserted - Intravitreal bevacizumab (2.5 mg/0.10 mL) was administered 3.5 mm or 4.0 mm from the limbus for pseudophakic or phakic eyes, respectively - Patients were randomized to either 27-gauge or 30-gauge needle	Pain was measured on a VAS from 0 to 10 and on the Wong-Baker FACES scale from 0 to 10. Pain was measured immediately after the intravitreal injection
Lourerio et al. (2017)	Portugal	Prospective single-center RCT	Patients were treatment-naïve and the anti-VEGF injection in the study was their first injection. Patients were excluded if any history of eye surgery other than for cataract, use of IOP-lowering drugs, corneal diseases, or complaints of ocular pain prior to the procedure	- Eye was cleaned with povidone-iodine - Oxybuprocaine 0.4% was instilled, povidone-iodine was instilled, and eye speculum was inserted - Intravitreal bevacizumab (1.5 mg/0.05 mL) was administered 3.5–4.0 mm from the limbus in the superotemporal quadrant - Patients were randomized to either 27-gauge or 30-gauge needle	Pain was measured with a VAS from 0 to 10. Pain was measured immediately after the intravitreal injection
Rodrigues et al. (2011)	Brazil	Prospective multi-center non-randomized comparative trial	Patients eligible for anti-VEGF therapy with any of the following diseases: AMD, diabetic retinopathy or maculopathy, retinal vein occlusion, inflammatory macular edema, choroidal neovascularization, polypoidal choroidal vasculopathy, central serous chorioretinopathy	- Eye was cleaned with povidone-iodine - Moxifloxacin was instilled - Tetracaine 0.5% was instilled three times - Eye speculum was inserted - Intravitreal bevacizumab (1.5 mg/0.05 mL) was administered 3.5 mm from the limbus in the superotemporal quadrant - Patients were allocated to 26-gauge, 27-gauge, 29-gauge, or 30-gauge needle	Pain was measured with a numeric scale ranging from 0 to 10. Pain was measured immediately after the intravitreal injection

Table 1 continued

Reference	Country	Design	Participant eligibility	Details of the anti-VEGF treatment	Pain measurement
Sasajima et al. (2018)	Japan	Prospective single-center RCT	Patients eligible for anti-VEGF therapy	- Eye was cleaned with povidone-iodine - Lidocaine 2% was instilled - Eye speculum was inserted - Intravitreal ranibizumab (0.5 mg/0.05 mL) or aflibercept (2 mg/0.05 mL) was administered 3.5–4.0 mm from the limbus in the superonasal or superotemporal quadrant - Injections were performed by surgeons - Patients were randomized to either 30-gauge or 34-gauge needle	Pain was measured with a numeric scale ranging from 0 to 10. Pain was measured immediately after the intravitreal injection
Van Asten et al. (2015)	Netherlands	Prospective single-center RCT	Patients with AMD, diabetic macular edema, or retinal vein occlusion eligible for at least two consecutive anti-VEGF injections within 6 weeks	- Eye was cleaned with povidone-iodine - Oxybuprocaine and tetracaine 1% was instilled. Further, an additional two rounds of povidone-iodine and tetracaine 1% were instilled - Eye speculum was inserted - Intravitreal bevacizumab was administered 3.5 mm or 4.0 mm from the limbus for pseudophakic or phakic eyes, respectively - Injections were performed by a surgeon - Randomization allocated the sequence of treatment, i.e., first the eye was treated using either the 30-gauge or 33-gauge needle according to the randomization, and the other gauge size was used at the next visit	Pain was measured with a numeric scale ranging from 0 to 10. Pain was measured immediately after the intravitreal injection

AMD, age-related macular degeneration; *Anti-VEGF*, anti-vascular endothelial growth factor; *IOP*, intraocular pressure; *RCT*, randomized controlled trial; *USA*, United States of America; *VAS*, visual analogue scale

Table 2 Characteristics of study groups in reviewed studies

Reference	Study groups	Age, years	Females, %	Anti-VEGF drug used, %	Numbers allocated (eyes/patients)	Numbers analyzed (eyes/patients)
Aderman et al. (2018)	30-gauge needle	–	–	–	49/49[a]	49/49[a]
	33-gauge needle	–	–	–	49/49[a]	49/49[a]
Alshahrani et al. (2021)	30-gauge needle	78 ± 11	42%	RNZ 100%	86/86	86/86
	32-gauge needle	78 ± 11	40%	RNZ 100%	86/86	86/86
Eaton et al. (2013)	30-gauge needle	–	–	–	70/70[a]	70/70[a]
	33-gauge needle	–	–	–	70/70[a]	70/70[a]
Güler et al. (2015)	27-gauge needle	65 ± 10	49%	BVZ 100%	35/35	35/35
	30-gauge needle	60 ± 12	54%	RNZ 100%	35/35	35/35
Haas et al. (2016)	27-gauge needle	72 ± 11	55%	BVZ 100%	104/104	104/104
	30-gauge needle	75 ± 11	52%	BVZ 100%	104/104	104/104
Lourerio et al. (2017)	27-gauge needle	70 ± 10	–	BVZ 100%	27/24	27/24
	30-gauge needle	69 ± 10	–	BVZ 100%	27/24	27/24
Rodrigues et al. (2011)	26-gauge needle	70 ± 13[b]	59%[b]	BVZ 100%	16/16	16/16
	27-gauge needle			BVZ 100%	23/23	23/23
	29-gauge needle			BVZ 100%	83/83	83/83
	30-gauge needle			BVZ 100%	83/83	83/83
Sasajima et al. (2018)	30-gauge needle	75 ± 13	35%	AFL 80%	69/[c]	69/[c]
				RNZ 20%		
	34-gauge needle	76 ± 8	30%	AFL 86%	71/[c]	71/[c]
				RNZ 14%		

Table 2 continued

Reference	Study groups	Age, years	Females, %	Anti-VEGF drug used, %	Numbers allocated (eyes/patients)	Numbers analyzed (eyes/patients)
Van Asten et al. (2015)	30-gauge needle	68 ± 13	36%	BVZ 100%	36/36[d]	36/36[d]
	33-gauge needle	68 ± 13	36%	BVZ 100%	36/36[d]	36/36[d]

Continuous data are expressed as mean ± standard deviation

AFL, aflibercept; *Anti-VEGF*, anti-vascular endothelial growth factor; *BVZ*, bevacizumab; *RNZ*, ranibizumab

[a]This study included patients with a need for bilateral intravitreal anti-VEGF injection for the entire study—one eye received intravitreal injection using the 30-gauge needle, the other eye using the 33-gauge needle

[b]This study only reported overall demographics and no gauge needle group-specific demographics

[c]This study included 140 eyes of 110 patients, and only reported the number of eyes in each group, not the number of patients

[d]This study included patients eligible for at least two intravitreal anti-VEGF injections within 6 weeks, and randomization allocated gauge needle groups to the sequence of treatment, i.e., first the eye was treated with either the 30-gauge or 33-gauge needle according to the randomization, and the other gauge size was used at the next visit

Five studies compared the 30-gauge needle with thinner needle sizes [23–25, 30, 31]. Aderman et al. compared the pain experience of treatment with 30-gauge and 33-gauge needles [23]. Patients received bilateral injections on the same day, one injection with each gauge size, and the order of the gauge size was randomized [23]. This study showed that significantly more patients preferred the thinner 33-gauge needle, but the difference in the pain score between the two gauge sizes was not statistically significant [23]. Alshahrani et al. randomized patients to treatment using either 30-gauge or 32-gauge needles [24], and found a lower pain score in patients treated with the thinner 32-gauge needle [24]. Both Aderman et al. and Alshahrani et al. explored the relationship between age, sex, and diagnosis and the pain experience, and neither study found any significant correlation [23, 24]. Eaton et al. compared the pain experience of treatment with 30-gauge and 33-gauge needles [25]. The patients were asked about their pain level during the injection, immediately after the injection, later the same day, and the next day—no significant differences were found between the two groups [25]. However, this study reported that the topical anesthesia strategy, and especially the use of subconjunctival anesthesia, led to lower pain scores [25]. Sasajima et al. randomized eyes into either 30-gauge or 34-gauge needles and found that patients reported lower pain on pain scores when the 34-gauge needle was used [30]. Van Asten et al. recruited patients with at least two consecutively planned injections and performed one of the injections with a 30-gauge needle and the other with a 33-gauge needle and randomized the order of the gauge sizes used [31]. This study found no statistically significant difference, and no change in the pain experience from one injection to the next [31]. A positive correlation was found between the pain experience and the following: experience of distress prior to the injection, negative view of the preparations for the injection, negative experience with prior injections, expected negative treatment outcomes, and lower belief that the injections would improve their health [31].

Fig. 2 Risk of bias of individual studies

Risk of Bias within Studies

Risk-of-bias evaluation was based on assignment to intervention (i.e., the intention-to-treat effect) and made on five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of the reported results) which together contributed to an overall risk-of-bias evaluation. The randomization process found a high risk of bias in two studies which did not randomize participants and some concerns in the remaining studies due to the lack of details of the randomization process. Some concerns were raised across all studies in the domain of deviations from intended interventions mainly because individuals delivering the interventions were aware of the participants' assigned intervention during the study. In the remaining domains, no concerns were found. The risk-of-bias evaluations within studies are summarized in Fig. 2.

Network Meta-Analyses

The network plot illustrates a complete network (Fig. 3). We used the largest gauge needle size in the network (26-gauge needle) as the reference group and compared the other gauge needle groups through direct and indirect comparisons within the network (Fig. 3). Pain experience from intravitreal anti-VEGF injections was ranked as follows (from the most to the least painful) and according to the difference in effect size (Cohen's *d*) as compared with the 26-gauge needle reference group (Fig. 3):

- 27-gauge needle (*d*: −0.4; 95% CI −1.9 to 1.2; $P = 0.66$)

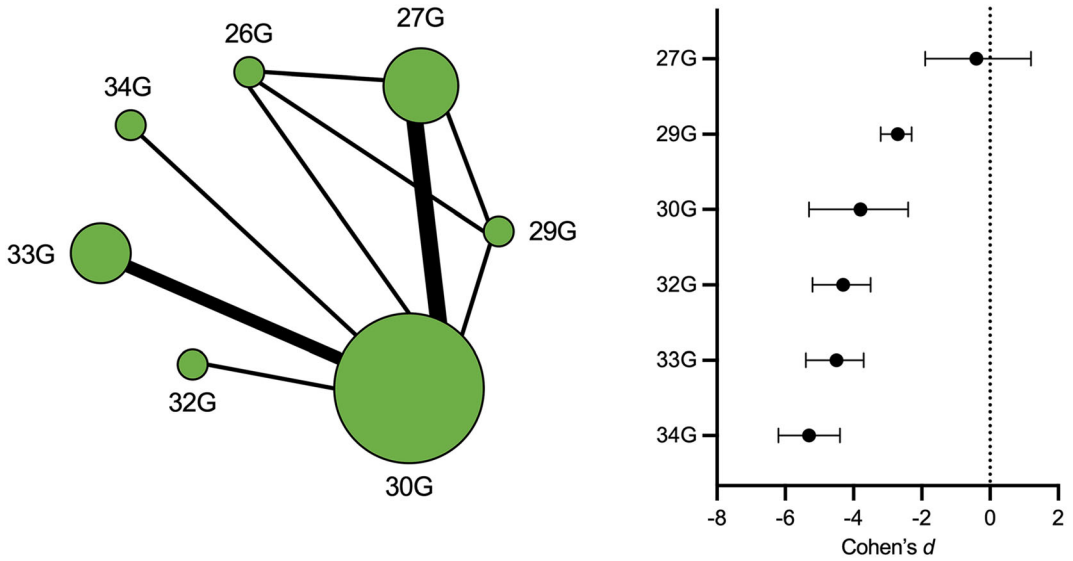

Fig. 3 Network meta-analysis of the effect of needle gauge size on pain after intravitreal anti-vascular endothelial growth factor injection. *Left:* Network plot illustrating comparisons in the meta-analysis. The size of the green dots indicates the number of studies including that specific needle gauge (G) size group. The thickness of the lines between the green dots corresponds to the number of direct comparisons between the needle gauge size groups within the network. *Right*: Summary estimates (dots and whiskers) for pain experience in each needle gauge size group are provided as standardized effect size (Cohen's *d*) relative to that of the 26G group (reference, indicated by the dotted line). A group is not statistically different from the reference if the confidence interval crosses the dotted line

- 29-gauge needle (*d*: −2.7; 95% CI −3.2 to −2.3; $P < 0.00001$)
- 30-gauge needle (*d*: −3.8; 95% CI −5.3 to −2.4; $P < 0.00001$)
- 32-gauge needle (*d*: −4.3; 95% CI −5.2 to −3.5; $P < 0.00001$)
- 33-gauge needle (*d*: −4.5; 95% CI −5.4 to −3.7; $P < 0.00001$)
- 34-gauge needle (*d*: −5.3; 95% CI −6.2 to −4.4; $P < 0.00001$)

Detailed summaries of each individually calculated direct and indirect estimate are available in Supplementary Material.

DISCUSSION

This systematic review and network meta-analysis of needle gauge sizes and pain experience found a clear relationship between thinner needle gauge sizes and lower pain experience from intravitreal injections. According to the interpretation of Cohen's *d*, the rule of thumb is that effect sizes are small at $d = 0.2$, moderate at $d = 0.5$, and large at $d = 0.8$ [32]. In that regard, we observe very large differences between the thicker 26-gauge and 27-gauge needles, and the thinner sizes of 30-gauge ($d = -3.8$), 32-gauge ($d = -4.3$), 33-gauge ($d = -4.5$), and 34-gauge ($d = -5.3$). Considering that intravitreal injections with anti-VEGF often require many treatments over years for patients [33–35], improving the patient experience in relation to the treatments is of great importance.

Our findings in this study follow the notions of published guidelines and expert consensus papers [16–18, 36–40]. The Euretina Expert Consensus Recommendations state that 30-gauge or thinner needles are recommended, but that larger needles can be employed when necessary [16]. The Royal College of Ophthalmologists state that 30-gauge needles are recommended [36]. The Royal Australian and New Zealand College of Ophthalmologists

recommend a 27-gauge needle for triamcinolone and a 30-gauge or thinner for other preparations [37]. The Intravitreal Injection Task Force Committee of the American Society of Retina Specialists recommends a gauge size of 30, 31, 32, or 33 [17]. The American Academy of Ophthalmology notes that 30-gauge needles are commonly used, and thinner needle sizes may decrease patient discomfort [38]. One expert update published in *Retina Specialist* recommends 30-gauge or thinner [39], and another guideline published in *Review of Ophthalmology* does not comment on gauge size [40]. One international practical approach paper recommends the use of 30-gauge needles [18].

Studies of pain show that the brain can generate the experience of pain even in the absence of input from peripheral nociceptors [41]. Pain experience is therefore a complex topic in which sensory input from peripheral nociceptors, for example, are processed together with affective and cognitive brain activity [41]. The complexity of the pain experience and the multifactorial influence on pain is also underscored by the definition of pain according to the International Association for the Study of Pain: "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [42]. In this regard, one would expect measurements of pain across studies to be associated with various factors not related to the injection procedure. Indeed, van Asten et al. explored these aspects in detail [31]. Greater pain experience was reported among patients who had an experience of distress prior to the injection, a negative view of the preparations for the injection, negative experience with prior injections, expected negative treatment outcomes, and lower belief that the injections would improve their health [31]. Thus, addressing pain related to intravitreal injections is a complex endeavor that also requires a holistic focus on the intravitreal injection service and the approach to the patients and addressing their fears, experiences, and expectations.

Limitations should be acknowledged when interpreting the results of this study. First, we only compared gauge sizes and disregarded analytically other aspects of preparation for the intravitreal injection. This limitation still allows comparisons throughout the network, as we are measuring differences between the groups that are randomized/compared according to the gauge size, i.e., the remaining aspects of preparations should remain similar between the groups within study. Still, however, it is likely that a topical anesthesia protocol applied in one study may differ significantly in anesthetic efficacy from a protocol applied in another study, which then may influence the difference between individual groups within studies that consequently challenges the extrapolation of results outside of individual studies. Second, pain is a complex sensation, and measuring it can be highly challenging. We used standardized mean differences to accommodate differences in tools used to measure pain. However, it is important to understand that the experience of pain can be influenced by a range of factors not necessarily related to the gauge size, which may introduce a challenge in accuracy when measuring pain. One can reasonably speculate that details of different protocols across studies, including the use of topical anesthesia, eye speculum, and povidone-iodine, may influence the results through a confounder effect. Further, aspects not outlined in the studies, such as music in the injection theater, having a neck pillow, patients having their hand held, or experiences in the waiting room/prior to entry to the clinic [31, 43], also have the potential to influence the results, and these aspects were not explored in our review. Controlling for some of these factors in a meaningful manner was not possible in our meta-analysis because of the heterogeneity of the preparation protocols across studies. Third, two studies did not randomize participants, and some concerns were raised across studies because individuals inquiring on the pain experience were aware of the intervention group. Finally, our conclusions are only as good as the studies that provide the data for our analysis. Although nine studies allow for robust analyses, additional studies and more direct comparisons across the groups would provide better certainty around the conclusions.

CONCLUSIONS

Our systematic review of the literature and network meta-analysis found a relationship between thinner needle gauge sizes and lower pain experience from intravitreal injections. Our findings are in line with the notions expressed in international guidelines and consensus papers for the administration of intravitreal anti-VEGF injections, and provide clear evidence for decreased pain with the use of 30-gauge or thinner needle sizes. In drug development, we recommend exploring the thinnest feasible gauge size to minimize patient discomfort.

Author Contributions. All authors (Emilie T. S. Butler, Jakob Bjerager, Nathalie S. Eriksen, Javad N. Hajari, Miklos Schneider, Carsten Faber, and Yousif Subhi) contributed to the study conception and design. Data acquisition and analysis were performed by authors Emilie T. S. Butler, Jakob Bjerager, Nathalie S. Eriksen, and Yousif Subhi. The first draft of the manuscript was written by authors Emilie T. S. Butler and Yousif Subhi, and all authors (Emilie T. S. Butler, Jakob Bjerager, Nathalie S. Eriksen, Javad N. Hajari, Miklos Schneider, Carsten Faber, and Yousif Subhi) commented on previous versions of the manuscript. All authors (Emilie T. S. Butler, Jakob Bjerager, Nathalie S. Eriksen, Javad N. Hajari, Miklos Schneider, Carsten Faber, and Yousif Subhi) read and approved the final manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

Conflict of Interest. Miklos Schneider has received investigator fees from Allergan, Bayer, Novartis, and Roche, has served as an advisory board member for Novartis and Roche, and has acted as consultant for AbbVie, not related to this work. Yousif Subhi has received speaker fees for lectures from Bayer and Roche, not related to this work. Emilie T. S. Butler, Jakob Bjerager, Nathalie S. Eriksen, Javad N. Hajari and Carsten Faber have nothing to disclose.

Ethical Approval. This study is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Bloch SB, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. Am J Ophthalmol. 2012;153:209–13.

2. Ferløv Baselius NJ, Brynskov T, Falk MK, Sørensen TL, Subhi Y. Driving vision in patients with neovascular AMD in anti-VEGF treatment. Acta Ophthalmol. 2021;99:e1360–5.

3. Review of Ophthalmology. IVT Injections: Health Policy Implications. Available from https://www.reviewofophthalmology.com/article/ivt-injections-health-policy-implications. Accessed 6 November 2023.

4. Jørstad ØK, Steffensen LA, Eriksen K, Bragadóttir R, Moe MC. Thirteen years of intravitreal anti-vascular endothelial growth factor therapy: the promises and burdens of a paradigm shift told from the perspective of the largest retina service in Norway. Acta Ophthalmol. 2020;98:774–9.

5. Thinggaard BS, Pedersen F, Grauslund J, Stokholm L. Intravitreal vascular endothelial growth factor inhibitor therapy in Denmark and 5-year projections. JAMA Netw Open. 2023;6: e2335148.

6. Casten R, Rovner BW, Leiby BE, Tasman W. Depression despite anti-vascular endothelial growth factor treatment of age-related macular degeneration. Arch Ophthalmol. 2010;128:506–8.

7. Droege KM, Muether PS, Hermann MM, et al. Adherence to ranibizumab treatment for neovascular age-related macular degeneration in real life. Graefes Arch Clin Exp Ophthalmol. 2013;251: 1281–4.

8. Müller S, Ehlken C, Bauer-Steinhusen U, et al. Treatment of age-related neovascular macular degeneration: the patient's perspective. Graefes Arch Clin Exp Ophthalmol. 2017;255:2237–46.

9. Senra H, Balaskas K, Mahmoodi N, Aslam T. Experience of anti-VEGF treatment and clinical levels of depression and anxiety in patients with wet age-related macular degeneration. Am J Ophthalmol. 2017;177:213–24.

10. Segal O, Segal-Trivitz Y, Nemet AY, Cohen P, Geffen N, Mimouni M. Anxiety levels and perceived pain intensity during intravitreal injections. Acta Ophthalmol. 2016;94:203–4.

11. Yiallouridou C, Acton JH, Banerjee S, Waterman H, Wood A. The experience of patients and practitioners of intravitreal anti-VEGF injection procedures and the associated factors. Invest Ophthalmol Vis Sci. 2020;61:4205.

12. McClard CK, Wang R, Windham V, et al. Questionnaire to assess life impact of treatment by intravitreal injections (QUALITII): development of a patient-reported measure to assess treatment burden of repeat intravitreal injections. BMJ Open Ophthalmol. 2021;6: e000669.

13. Mekala S, Dhoble P, Vishwaraj CR, Khodifad AM, Hess OM, Lavanya GS. Subjective and objective measures of the patient experience before, during, and after intravitreal anti-vascular endothelial growth factor injections. Indian J Ophthalmol. 2021;69:890–4.

14. Reitan G, Kjellevold Haugen IB, Andersen K, Bragadottir R, Bindesbøll C. Through the eyes of patients: understanding treatment burden of intravitreal anti-VEGF injections for nAMD patients in Norway. Clin Ophthalmol. 2023;17:1465–74.

15. Subhi Y, Sørensen TL. Neovascular age-related macular degeneration in the very old (≥90 Years): epidemiology, adherence to treatment, and comparison of efficacy. J Ophthalmol. 2017;2017: 7194927.

16. Grzybowski A, Told R, Sacu S, et al. 2018 update on intravitreal injections: euretina expert consensus recommendations. Ophthalmologica. 2018;239: 181–93.

17. Lam LA, Mehta S, Lad EM, Emerson GG, Jumper JM, Awh CC. Task force on intravitreal injection supplemental services (2021): intravitreal injection therapy: current techniques and supplemental services. J Vitreoretin Dis. 2018;5:438–47.

18. Petri AS, Boysen K, Cehofski LJ, et al. Intravitreal injections with vascular endothelial growth factor inhibitors: a practical approach. Ophthalmol Ther. 2020;9:191–203.

19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2020;339:b2535.

20. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook. Accessed 4 November 2023.

21. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366: l4898.

22. Doi SAR, Barendregt JJ. A generalized pairwise modelling framework for network meta-analysis. Int J Evid Based Healthc. 2018;16:187–94.

23. Aderman CM, Rahimy E, Obeid A, et al. Comparing 33-Gauge versus 30-gauge needles for intravitreal injections. Ophthalmol Retina. 2018;2:1078–9.

24. Alshahrani ST, Rubin U, Gupta V, Gonder T, Sharma S. Reflux, intraocular pressure variation and pain following intravitreal ranibizumab injections using 30-gauge or 32-gauge needles for patients with retinal pathologies: a randomized clinical trial. Cureus. 2021;13: e14320.

25. Eaton AM, Gordon GM, Wafapoor H, Sgarlata A, Avery RL. Assessment of novel guarded needle to increase patient comfort and decrease injection time during intravitreal injection. Ophthalmic Surg Lasers Imaging Retina. 2013;44:561–8.

26. Güler M, Bilgin B, Çapkın M, Şimşek A, Bilak Ş. Assessment of patient pain experience during intravitreal 27-gauge bevacizumab and 30-gauge ranibizumab injection. Korean J Ophthalmol. 2015;29:190–4.

27. Haas P, Falkner-Radler C, Wimpissinger B, Malina M, Binder S. Needle size in intravitreal injections—pain evaluation of a randomized clinical trial. Acta Ophthalmol. 2016;94:198–202.

28. Loureiro M, Matos R, Sepulveda P, Meira D. Intravitreal injections of bevacizumab: the impact of needle size in intraocular pressure and pain. J Curr Glaucoma Pract. 2017;11:38–41.

29. Rodrigues EB, Grumann A Jr, Penha FM, et al. Effect of needle type and injection technique on pain level and vitreal reflux in intravitreal injection. J Ocul Pharmacol Ther. 2011;27:197–203.

30. Sasajima H, Tsuboi K, Ono H, Murotani K, Kamei M. A randomized trial of a short 34-gauge needle for intravitreal injections. Ophthalmology. 2018;125:947–8.

31. van Asten F, van Middendorp H, Verkerk S, et al. Are intravitreal injections with ultrathin 33-G needles less painful than the commonly used 30-G needles? Retina. 2015;35:1778–85.

32. Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol. 2013;4:863.

33. Potapenko I, la Cour M. Modelling and prognostication of growth in the number of patients treated for neovascular age-related macular degeneration. Acta Ophthalmol. 2021;99:e1348–53.

34. Subhi Y, Potapenko I, Hajari JN, la Cour M. Anti-VEGF treatment of diabetic macular edema in Denmark: incidence, burden of therapy, and forecasting analyses. J Pers Med. 2023;13:546.

35. Subhi Y, Potapenko I, Hajari JN, la Cour M. Prognostic modelling of number of patients with retinal vein occlusion in anti-VEGF therapy. Acta Ophthalmol 2023. https://doi.org/10.1111/aos.15721. (ePub ahead of print 2023 Jun 6)

36. The Royal College of Ophthalmologists. Ophthalmic service guidance: intravitreal injection therapy. Available from https://curriculum.rcophth.ac.uk/wp-content/uploads/2018/02/Intravitreal-Injection-Therapy-August-2018-2.pdf. Accessed 4 November 2023.

37. The Royal Australian and New Zealand College of Ophthalmologists. Guidelines for Performing Intravitreal Therapy. https://ranzco.edu/wp-content/uploads/2018/11/IVI-Guidelines-for-Performing-Intravitreal-Therapy-2017. Accessed 4 November 2023.

38. American Academy of Ophthalmology. How to give intravitreal injections. Available from https://www.aao.org/eyenet/article/how-to-give-intravitreal-injections. Accessed 4 November 2023.

39. Retina Specialist. An update on the intravitreal injection procedure. Available from https://www.retina-specialist.com/article/an-update-on-the-intravitreal-injection-procedure. Accessed 4 November 2023.

40. Review of Ophthalmology. Updated guidelines for intravitreal injection. Available from https://www.reviewofophthalmology.com/article/updated-guidelines-for-intravitreal-injection. Accessed 4 November 2023.

41. Loeser JD. Melzack R. Pain: an overview. Lancet. 1999;353:1607–9.

42. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161:1976–82.

43. Gomez J, Koozekanani DD, Feng AZ, et al. Strategies for improving patient comfort during intravitreal injections: results from a survey-based study. Ophthalmol Ther. 2016;5:183–90.