Non-physician delivered intravitreal injection service is feasible and safe – a systematic review

Asrin Rasul[1], Yousif Subhi[1, 2], Torben Lykke Sørensen[1, 2] & Inger Christine Munch[1, 2]

ABSTRACT

INTRODUCTION: Non-physicians such as nurses are trained to give injections into the vitreous body of the eye to meet the increasing demand for intravitreal therapy with vascular endothelial growth factor inhibitors against common eye diseases, e.g. age-related macular degeneration and diabetic retinopathy. We systematically reviewed the existing literature to provide an overview of the experiences in this transformational process.

METHODS: We searched for literature on 22 September 2015 using PubMed, Embase, the Cochrane Library, CINAHL and the Web of Science. Eligible studies had to address any outcome based on non-physician delivered intravitreal therapy regardless of the study design. Being non-physician was defined as the injecting personnel n ot being a physician, but no further restrictions were made.

RESULTS: Five studies were included with a total of 31,303 injections having been performed by 16 nurses. The studies found that having nurses perform the intravitreal injections produced to a short-term capacity improvement and liberated physicians for other clinical work. Training was provided through courses and direct supervision. The rates of endophthalmitis were 0-0.40‰, which is comparable to reported rates when the intravitreal therapy is given by physicians.

CONCLUSION: Non-physician delivered intravitreal therapy seems feasible and safe.

Intravitreal therapy with vascular endothelial growth factor inhibitors was introduced on a wide scale in Denmark in 2007 and has since fundamentally changed the prognosis of a range of retinal diseases such as wet age-related macular degeneration (AMD) [1-4], diabetic macular oedema (DME) [5], retinal vein occlusion (RVO) [6] and myopic choroidal neovascularisations [7]. AMD, DME and RVO are common diseases with AMD being the most frequent cause of irreversible vision loss and social blindness amongst the elderly in the Western World [8-12]. The approximate global number of patients with AMD is estimated to reach 200 million in 2020 and 300 million in 2040 [13]. Projection studies forecast that the number of patients in need of intravitreal injection therapy in Denmark will continue to increase at least until 2050 due to an increasing number of elderly that also live longer [14]. This is in line with our experiences from daily clinical practice where the number of intravitreal injections has increased every year since 2007 [15]. Phase II and III trials using intravitreal injections are ongoing and may further broaden the range of indication, e.g. for dry AMD [16] and proliferative diabetic retinopathy [17]. Thanks to intravitreal therapy with anti-VEGF, the number of people who are socially blind from AMD decreases in developed countries including Denmark [9, 10, 18]. Timely initiation of treatment is crucial for the prognosis, and treatment delay may impair vision significantly and irreversibly [18-22], underscoring the importance of availability.

The intravitreal injection procedure is quite simple. The injection is given through the pars plana of the retina, typically 3.5-4 mm superotemporally from the limbus, and the medicine is injected into the vitreous body of the eye using a 30-gauge needle (**Figure 1**). The injections are given at regular intervals of 4-8 weeks depending on the drug, the underlying disease and the clinically measured disease activity [23]. The need for repeated injections and still broader indications for intravitreal injection therapy combined with the limited availability of ophthalmologists especially in rural areas challenge our daily clinical planning. The intravitreal injection service is in a fragile position with very few health workers committing long-term to this ever-growing area.

The simple nature of the procedure and the low prevalence of complications have triggered considerations as to the feasibility of training non-physicians to perform the injections [24]. A key element is that although intravitreal injection is a very safe procedure, the rarely occurring complications can be devastating [25]. An infection within the eye, i.e. endophthalmitis, may lead to severe vision loss and even enucleation of the eye; and traumatic cataract and retinal pigment epithelial tear are other important complications that threaten patients' vision. Some health workers possess relevant medical training and may therefore be well suited for delivering intravitreal injections, especially nurses who are trained in aseptic technique and administration of injections in general.

To provide an overview of this growing field, we systematically reviewed the published literature on experiences with non-physician intravitreal injection therapy.

SYSETMATIC REVIEW

1) Department of Ophthalmology, Zealand University Hospital, Roskilde
2) Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Dan Med J 2016;63(5):A5229

FIGURE 1

Intravitreal injection treatment is a common procedure in ophthalmology departments.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews [26]. Our aim was to include studies reporting on experiences with non-physician delivered intravitreal injection therapy.

All original studies were included, regardless of study design. Studies had to address any outcome based on non-physician delivered intravitreal injection therapy. Being non-physician was defined as the injecting personnel not being a physician, but no further restrictions were used. Case studies or comments were not included. Eligibility was restricted to studies in English.

We searched the literature using the electronic bibliographic databases of PubMed, EMBASE, the Cochrane Library, CINAHL and the Web of Science on 22 September 2015. We used the following search strategy: (nurse OR orthoptists OR optometrist OR non-physician) AND (intravitreal).

All references were screened by title and abstract by one author (YS) who excluded irrelevant references, duplicates and studies not written in English. No date restrictions were applied. All remaining references were retrieved in full-text. Full-text articles were read for eligibility and data extraction by two authors (AR and YS) and references of all included studies were read to find additional eligible studies. We extracted details on study meta-data (title, authors, year of publication, country), study design (eligibility criteria, number of injections, setting and methods), study results (number of injections and capacity change, implementation and training experiences, safety, and patient-centred outcomes). Potential bias for each included study was assessed using the Critical Appraisal Skills Programme checklists that help systematically assess study quality through a set of questions [27]. Studies were included in a qualitative analysis to provide an overview of the existing literature. After reading the included studies, four topics were identified which we used to systematise the presentation of the review.

RESULTS

Studies identified in the systematic review

Our search yielded 59 records of which 30 were duplicates and 21 were irrelevant. A total of 8 records were therefore retrieved in full-text. Four studies were deemed eligible, and one additional study was identified from the reference lists. In total, five studies were included in this systematic review (**Figure 2**). Studies included a total of 31,303 injections performed by 16 nurses [28-32] (**Table 1**). All studies used nurses for non-physician intravitreal injection therapy [28-32]. A total of four studies were based on experiences from the United Kingdom [28, 30-32] and one was based on experiences from Denmark [29]. Three studies were prospective [30-32] and two were retrospective [28, 29]. One study provided short-term (five months) results [32], while the rest provided long-term (17 months-5.5 years) results [28-31]. Two studies described the change in intravitreal injection service capacity [28, 30]. All five studies described implementation and training aspects and reported on safety parameters [28-32]. Three studies reported on patient-centred outcomes [28, 30, 32].

Number of injections and capacity improvements

Two studies described intravitreal injection service capacity after the implementation of nurse-delivered intravitreal injection therapy [28, 30]. In one study, nurse-delivered intravitreal injection therapy implemented for patients with neovascular AMD led to a 25% increase in the number of treatments given during a five-month

KEY POINTS

- Intravitreal injection therapy is used against a range of common eye diseases, for which it changes the prognosis fundamentally.
- For the majority of patients, intravitreal injection therapy is needed regularly, timely, and for many years, which accumulates the number of patients in treatment. Combined with an absolute and relative increase in the number of aged individuals in the Western World, these facts lead to an ever-increasing demand for therapy that is challenging to meet in terms of physician staffing
- One solution for this problem may be to train non-physicians such as nurses to give the intravitreal injections. Experiences with these transformational changes have been documented in the literature, which we here review (five studies with a total of 31,303 injections performed by 16 nurses).
- Non-physician delivered intravitreal therapy was possible through training and supervision, it boosted capacity and liberated physicians for other clinical work, without compromising on safety.

period [28]. The other study reported experiences from two hospitals which before the implementation had problems with adequate staffing and had to use medical staffing agencies three times weekly. After the implementation of nurse-delivered intravitreal injection therapy, use of medical staffing agencies decreased and the retinal specialists at both hospitals were liberated for other clinical work [30]. This study did not report on number of treatments before and after the implementation [30].

Implementation and training

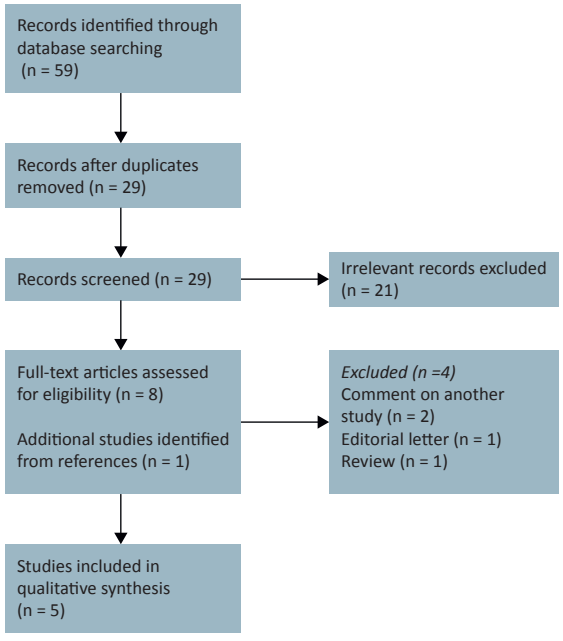
All five studies described implementation and training aspects [28-32]. The four reports from United Kingdom stressed that approval from hospital governance and relevant committees were needed [28, 30-32]. A business case and a design for a formal training programme were written specifically for the nurse-delivered intravitreal injection therapy service [28, 30-32]. Some centres prepared patient information leaflets to inform the patients that nurses would be giving the intravitreal injections and patients had to sign a consent form giving permission to have a nurse administering the injection [28, 31]. Two ophthalmology departments in United Kingdom (Royal Bolton Hospital and East Lancashire Hospital) invited patients to choose between receiving the intravitreal injection by a physician or a nurse [30]. At one Danish site (Glostrup Hospital), both nurse- and physician-delivered intravitreal injection service were available at the same time and only patients without poor cooperation, previous complications, concomitant eye diseases or significant disabilities were allocated to the nurse-delivered intravitreal injection service [29]. The consultant ophthalmologists retained the clinical responsibility for the patient [28, 32].

Senior nurses and nurses with extensive surgical or ophthalmological background were selected for training [28, 30-32], e.g. nurses had observed 1,000-1,500 intravitreal injections or had regularly assisted in ophthalmic surgery. One study did not describe a specific level of experience among nurses [29]. Training was managed by vitreoretinal surgeons, medical retinal specialists or other physicians with specialist expertise [28-32]. Training included theoretical lectures and practical exercises. Some centres used a formalised course with recommended textbooks and wet labs [28, 29, 32], whereas at other centres the nurses were trained on a one-to-one basis with direct observation and supervision [30, 31]. Wet labs and eye models were used for training the identification of the injection site, the angle of needle insertion and the insertion itself [28, 29, 32]. After relevant training, injections were given under supervision until a pre-specified number of injections (8-200 injections) had been performed to satisfaction or until the supervisor deemed that the injector could function independently [28-32]. Different approaches were used to ensure training outcome besides supervisor satisfaction – some nurses underwent an overall competency assessment [28] and other nurses had to pass a competency assessment step-wise for each of the elements in intravitreal injection therapy before the nurse was allowed to proceed to the next step [32].

Complications and safety

All five studies reported on safety parameters [22-26] (Table 1). The incidence of endophthalmitis was reported to be between 0-0.40‰ [28-32]. Two studies had data on both nurse- and physician-delivered intravitreal injections [28, 29]. The incidence rates of endophthalmitis were comparable between physicians (0-0.42‰) and nurses (0.32-0.40‰) [28, 29], although the allocation of patients into nurse- or physician-delivered intravitreal injections was influenced by parameters that likely could have biased the results (the patients' ability to cooperate, existence of concomitant eye diseases, any general disabilities and previous complications) [29]. Other major adverse events were uveitis, traumatic cataract, vitreous haemorrhage, retinal detachment and retinal pigment epithelial tears, which were reported at an even lower rate than endophthalmitis [28-32]. Minor adverse events were also reported in two studies with incidences of subconjunctival haemorrhage between 0-57‰ and corneal problems between 3.6-5.0‰ [30, 32].

FIGURE 2



Selection process of studies screened and evaluated for eligibility.

TABLE 1

Detailed overview of the included studies.

Reference	Site	Design	Setting	Non-physician characteristics	Supervised injections, n	Reported domains	Injections, n	Prevalence of injection-related adverse events among non-physicians, ‰
DaCosta et al, 2014 [28]	Medical Retina Service, Moorfields Eye Hospital, UK	Retrospective cohort: 2 yrs	Operating room	3 nurse practitioners trained in a 1-day course after which they observed practice	20	Injections: n Implementation: description Complications: n Patient experience: survey	4,000	Endophthalmitis: 0 Cataract: 0 Loss of central artery perfusion: 0 Uveitis: 0 Retinal detachment: 0 Vitreous haemorrhage: 0 Subconjunctival haemorrhage: 57
Hasler et al, 2015 [29]	Department of Ophthalmology, Glostrup Hospital, Denmark	Retrospective cohort: 5 yrs	Operating room	4 nurses trained by vitreoretinal surgeons	8-10	Injections: n Complications: n	12,542	Endophthalmitis: 0.032
Michelotti et al, 2014 [30]	Ophthalmology Departments of Royal Bolton Hospital NHS Foundation Trust and East Lancashire NHS Foundation Trust, UK	Prospective cohort: 17 mo.	Operating room	2 nurse practitioners and 1 senior nurse were trained and supervised by ophthalmologist	200	Injections: n Implementation: description Complications: n Patient experience: survey	3,355	Endophthalmitis: 0 Retinal tears: 0 Retinal detachment: 0 Vitreous haemorrhage: 0 Subconjunctival haemorrhage and corneal abrasion: 3.6
Simcock et al, 2014 [31]	West of England Eye Unit, Royal Devon & Exeter NHS Foundation Trust, UK	Prospective cohort: 5.5 yrs	Operating room	2 nurse practitioners trained 1-on-1 by a vitreoretinal surgeon	20	Injections: n Implementation: description Complications: n	10,006	Endophthalmitis: 0.40
Varma et al, 2013 [32]	Sunderland Eye Infirmary, UK	Prospective cohort: 5 mo.	Operating room	4 nurses with surgical backgrounds trained in a 1-day course	25	Injections: n Implementation: description Complications: n Patient experience: survey and pain score	1,400	Endophthalmitis: 0 Cataract: 0 Retinal detachment: 0 Exacerbation of blepharitis: 0.71 Corneal punctate epitheliopathy: 5.0 Subconjunctival haemorrhage: 8.6

Patient-centred outcomes

Three studies described patient-centred outcomes [28, 30, 32]. One study looked at reasons for declining having injections performed by nurses and at results from a satisfaction questionnaire filled out by patients willing to be treated by nurses [28]. A total of ten out of 100 patients declined injections by nurses in the pilot phase of the study and the reasons given were anxiety due to lack of experience of the nurse and preference for a physician. In all, 50 patients filled out the satisfaction questionnaire after having received intravitreal injection therapy by nurses. The overall score was high with 62% of patients reporting complete satisfaction in all elements of care with a maximal score of 5/5 and 38% patients being satisfied with all elements of care with a score of 4/5 for all questions answered [28]. Another study did not report quantitatively on patient satisfaction, but stated that patient waiting time was reduced, that physicians had more time to review patients for treatment control within the recommended guidelines and that they had received positive formal and informal feedback [30].
A third study reported on patient-perceived pain in relation to intravitreal injections [32]. On a pain scale from 0 (no pain) to 5 (worst pain), 96.5% of the patients gave a pain score of 0 or 1 [32]. None of the studies compared patient-centred outcomes between nurse-delivered and physician-delivered intravitreal injection therapy.

DISCUSSION

Injection with medicine directly into the vitreous body of the eye is a common clinical procedure with rare but devastating complications [25], and it is currently being delegated to non-physicians in an attempt to meet the increasing demands for intravitreal therapy. In this systematic review, we identified five studies reporting on experiences with non-physician administered intravitreal therapy which found that it was feasible to train nurses to deliver intravitreal injections and that safety was not compromised.

Endophthalmitis rates after intravitreal injections have been reported in the 0.00-0.50‰ range when given by physicians in operating room settings [25], which is comparable to the highest rate of 0.40‰ reported in the studies with nurses performing the injections. However, at rates in the 0-0.50‰ range, high sample sizes are required to achieve a representative picture of the endophthalmitis rates [25] – e.g. studies on physicians included 7,584-40,001 injections, a range

which only two studies in this review reached [29, 31]. One study reported that only non-problematic patients (able to cooperate, no concomitant eye diseases, no general disabilities and no previous complications) were allocated to non-physicians [31], which introduces a selection bias that should be considered when comparing complication rates between physicians and non-physicians.

The capacity improvement [28] and the ability to liberate physicians for other clinical work [30] may mean that non-physician delivered procedures can help us meet the increasing demand for intravitreal therapy. The short-term capacity improvement [28] suggests that the increase in demand for therapy may be hard to meet without using non-physicians. These changes may also lower the overall cost of intravitreal therapy, unless the training of the non-physicians is insufficient or the time consumption per patient increases. Thus, achieving these results may depend on how well non-physicians are trained and how the responsibility structure is set [28-32]. However, existing studies are merely descriptive, and we need studies that explore and compare implementation and training strategies, which in other areas of ophthalmology have been able to provide clear messages on optimal implementation and training [33, 34].

Developments in syringe design and delivery assist devices may further streamline and ease intravitreal injection therapy which may, in turn, ease transition into a non-physician delivered intravitreal injection service. Pre-filled syringes reduce preparation time by eliminating preparation steps that are subject to variation and pose a risk of contamination [35, 36]. InVitria (FCI Ophthalmics, Massachusetts, USA) is a clear polycarbonate mould designed to fit around the cornea and assist injection at a 3.5 mm distance from the limbus and at a 28° angle through a guide tube [37]. The guide tube also prevents eyelashes and the eyelid from touching the injecting needle [37], which should at least theoretically reduce the risk of endophthalmitis. Finally, a number of clinical trials explore the efficiency of new long-acting vascular endothelial growth factor inhibitor therapies [38], which may in future influence how intravitreal therapy is delivered and how many injections are needed per patient.

The limitations of this systematic review include the fact that only few published studies on non-physician intravitreal injection therapy services exist and hence only five studies could be included in this review. Furthermore, the conclusions of this review are based on results from studies with either no comparison groups or comparison groups with a severe selection bias. Participating nurses were experienced nurses, and results using inexperienced nurses may be different.

In conclusion, intravitreal therapy delivered by experienced nurses trained in the procedure is feasible and safe. We urge clinics who are implementing or have already implemented non-physician delivered intravitreal injection therapy to share their experiences and results.

CORRESPONDENCE: *Yousif Subhi.* E-mail: ysubhi@gmail.com

ACCEPTED: 24 February 2016

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

LITERATURE

1. Rosenfeld PJ, Brown DM, Heier JS et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419-31.
2. Brown DM, Kaiser PK, Michels M et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355: 1432-44.
3. Krüger Falk M, Kemp H, Sørensen TL. Four-year treatment results of neovascular age-related macular degeneration with ranibizumab and causes for discontinuation of treatment. Am J Ophthalmol 2013;155:89-95.
4. Subhi Y, Henningsen GØ, Larsen CT et al. Foveal morphology affects self-perceived visual function and treatment response in neovascular age-related macular degeneration: a cohort study. PLoS One 2014;9: e91227.
5. Korobelnik JF, Do DV, Schmidt-Erfurth U et al. Intravitreal Aflibercept for diabetic macular edema. Ophthalmology 2014;121:2247-54.
6. Brown DM, Campochiaro PA, Singh RP et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010;117:1124-33.
7. Tufail A, Narendran N, Patel PJ et al. Ranibizumab in myopic choroidal neovascularization: the 12-month results from the REPAIR study. Ophthalmology 2013;120:1944-5.
8. Bourne RR, Stevens GA, White RA et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Glob Health 2013;1:e339-49.
9. Skaat A, Chetrit A, Belkin M et al. Time trends in the incidence and causes of blindness in Israel. Am J Ophthalmol 2012;153:214-21.
10. 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.
11. Buch H, Vinding T, Nielsen NV. Prevalence and causes of visual impairment according to World Health Organization and United States criteria in an aged, urban Scandinavian population: the Copenhagen City Eye Study. Ophthalmology 2001;108:2347-57.
12. Buch H, Vinding T, La Cour M et al. Prevalence and causes of visual impairment and blindness among 9980 Scandinavian adults: the Copenhagen City Eye Study. Ophthalmology 2004;111:53-61.
13. Wong WL, Su X, Li X et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health 2014;2:e106-16.
14. Lindekleiv H, Erke MG. Projected prevalence of age-related macular degeneration in Scandinavia 2012-2040. Acta Ophthalmol 2013;91:307-11.
15. Munch IC, Aria SA. [Injection of medicine in the eye against AMD]. Værn om Synet 2015;2:4-10.
16. Rafique I, Munch IC. New perspectives for the treatment of age-related macular degeneration. Ugeskr Læger 2013;175:2035-8.
17. Gross JG, Glassman AR, Jampol LM et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA 2015;314:2137-46.
18. Wong TY, Chakravarthy U, Klein R et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. Ophthalmology 2008;115:116-26.
19. Rasmussen A, Brandi S, Fuchs J et al. Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. Acta Ophthalmol 2015;93:616-20.
20. Muether PS, Hermann MM, Koch K et al. Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. Graefes Arch Clin Exp Ophthalmol 2011;249:633-7.
21. Rauch R, Weingessel B, Maca SM et al. Time to first treatment: the significance of early treatment of exudative age-related macular degeneration. Retina 2012;32:1260-4.
22. Muether PS, Hoerster R, Hermann MM et al. Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2013;251:453-8.
23. Stewart MW. Individualized treatment of neovascular age-related macular degeneration: What are patients gaining? Or losing? J Clin Med 2015;4: 1079-101.
24. Moorfields unveils new one-day course on setting up a nurse-led intravitreal injection service. www.moorfields.nhs.uk/news/moorfields-unveils-

new-one-day-course-setting-nurse-led-intravitreal-injection-service (22 Sep 2015).
25. Brynskov T, Kemp H, Sørensen TL. No cases of endophthalmitis after 20,293 intravitreal injections in an operating room setting. Retina 2014;34:951-7.
26. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
27. Critical Appraisal Skills Programme checklists. www.casp-uk.net/#!checklists/cb36 (22 Sep 2015).
28. DaCosta J, Hamilton R, Nago J et al. Implementation of a nurse-delivered intravitreal injection service. Eye (Lond) 2014;28:734-40.
29. 29. Hasler PW, Bloch SB, Villumsen J et al. Safety study of 38,503 intravitreal ranibizumab injections performed mainly by physicians in training and nurses in a hospital setting. Acta Ophthalmol 2015;93:122-5.
30. Michelotti MM, Abugreen S, Kelly SP et al. Transformational change: nurses substituting for ophthalmologists for intravitreal injections – a quality-improvement report. Clin Ophthalmol 2014;8:755-61.
31. Simcock P, Kingett B, Mann N et al. A safety audit of the first 10 000 intravitreal ranibizumab injections performed by nurse practitioners. Eye (Lond) 2014;28:1161-4.
32. Varma D, Lunt D, Johnson P et al. A novel approach to expanding the role of nurses to deliver intravitreal injections for patients with age-related macular degeneration. Int J Ophthalmic Pract 2013;4:68-74.
33. Sanders DS, Read-Brown S, Tu DC et al. Impact of an electronic health record operating room management system in ophthalmology on documentation time, surgical volume, and staffing. JAMA Ophthalmol 2014;132:586-92.
34. Thomsen AS, Subhi Y, Kiilgaard JF et al. Update on simulation-based surgical training and assessment in ophthalmology: a systematic review. Ophthalmology 2015;122:1111-30.
35. Subhi Y, Kjer B, Munch IC. Syringe preparation time with prefilled syringes and vials for intravitreal therapy. Dan Med J (submitted).
36. Souied E, Nghiem-Buffet S, Leteneux C et al. Ranibizumab prefilled syringes: benefits of reduced syringe preparation times and less complex preparation procedures. Eur J Ophthalmol 2015;25:529-34.
37. Ratnarajan G, Nath R, Appaswamy S et al. Intravitreal injections using a novel conjunctival mould: a comparison with a conventional technique. Br J Ophthalmol 2013;97:395-7.
38. Pecen PE, Kaiser PK. Current phase 1/2 research for neovascular age-related macular degeneration. Curr Opin Ophthalmol 2015;26:188-93.