DOI 10.5935/0034-7280.20210029

Overview of Cochrane systematic review about retinal detachment

Visão geral das revisões sistemáticas Cochrane em descolamento de retina

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Abstract

Retinal detachment (RD) is a common ophthalmic emergency that could bring permanent blindness if it is untreated or treatment is delayed. We conducted a review of Cochrane systematic reviews regarding retinal detachment interventions after a search strategy, we showed and analyzed the data narratively in Ophthalmologic Departure of Escola Paulista de Medicina-UNIFESP. As result, the group of pneumatic retinopexy was less susceptible to choroidal detachment and myopic shift as adverse events when compared with scleral buckle. Although there is no statistically significant difference in visual acuity between standard and heavy silicone oil and between C3F8 and silicone oil, the following interventions may present some benefits for RD: (a) LMWH with 5-FU versus placebo at high-risk of developing postoperative proliferative vitreoretinopathy (PVR); (b) silicone oil was favorable for macular attachment at 2 years compared to sulfur hexafluoride (SF6); (c) Retinal redetachment was reported in fewer participants in the Pars plana vitrectomy (PPV) group compared to the scleral buckling group. So, these points can be considered when choosing the technique to improve better results in cases of retinal detachment. In addition, there is still a need for studies with a prophylactic RD approach and studies with greater evidence of which surgical technique is most appropriate for each indication of RD considering the economic cost and the patient's quality of life.

Keywords: *Retinal detachment; Therapeutics; Evidence-based medicine; Evidence-based practice*

Resumo

Descolamento de retina (DR) é uma emergência oftalmológica comum que pode evoluir como uma das causas de cegueira se não for tratada ou tiver o tratamento demorado. Esta é uma revisão de revisões sistemáticas da Cochrane sobre descolamento de retina, relacionada às intervenções realizadas no tratamento do DR, após uma estratégia de busca apresentamos e analisamos os dados narrativamente conduzida no departamento de oftalmologia da Escola Paulista de Medicina-UNIFESP. Como resultado, o grupo de retinopexia pneumática foi menos suscetível ao descolamento de coroide e miopização como efeito adverso em comparação ao grupo de introflexão escleral. Apesar de não ter diferença estatisticamente significante entre a acuidade visual entre o uso de óleo de silicone padrão versus pesado, nem entre C3F8 e óleo de silicone, as seguintes intervenções apresentaram benefícios para o tratamento: (a) Heparina de baixo peso molecular com 5 fluorouracil diminuíram o risco de evoluir com proliferação vítreo-retiniana; (b) Uso de silicone foi mais favorável como substituto vítreo na fixação macular em 2 anos comparado com o uso de hexafluoreto de enxofre; (c) Novo descolamento de retina foi menor em pacientes submetidos a Vitrectomia pars plana comparada ao grupo de introflexão escleral. Portanto, esses dados podem ser considerados na escolha da técnica empregada para obter melhores resultados nos casos de DR. Além disso, existe a necessidade de estudos de alto nível de evidência em busca do procedimento cirúrgico mais apropriado e profilático para DR, levando em consideração custo-benefício e qualidade de vida.

Descritores; Descolamento de retina; Terapêutica; Medicina baseada em evidências; Prática baseada em evidências

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The author declare no conflict of interest

Received for publication 1/7/2020 - Accepted for publication 30/10/2020.

Introduction

Retinal detachment (RD) refers to the separation of the neurosensory retina (NSR) from the underlying retinal pigment epithelium (RPE) causing fluid accumulation within this potential space. There are four major types of RD, which are classified according to pathogenetic mechanisms: rhegmatogenous, tractional, exudative and combined tractional/rhegmatogenous retinal detachment.[1] Primary rhegmatogenous retinal detachment (RRD) represents the main subgroup and most frequent form of RD whose cause of the separation of the inner layers from pigment epithelial layer is a break in which a tear or a hole allowing the liquefied vitreous get into subretinal space.[2]

The RRD affects 0.6 to 1.8 people per 10,000 per year worldwide and can be a potential cause of blindness if not treated or treated late.[3] The incidence is concentrated in the two peaks of age group, the highest one is between 60 to 69 years old with increased of posterior vitreous detachment (PVD) and cataract surgery, considered risk factors to RD in this age group. The second age peak is younger between 20 to 30 years, especially in high myopics patients that can present more frequently atrophic holes and lattice degeneration.[4]

Once RRD is detected, surgical treatment should be carried out as soon as possible for a better result. Careful examination is essential to find all breaks, since the surgical objective is to irritate the tissues around each break and, thus, create an approximation and adhesion between the retina and the choroid. Some methods can be used for this purpose: laser, cryotherapy, or diathermy, and can be associated with vitrectomy, scleral buckling, pneumatic retinopexy techniques.[5]

The decision about which treatment approach depends on the surgeon, the location and number of the retinal breaks and the patient's phakic status. Patients with small holes, demarcation lines, no macular involvement and without proliferative vitreoretinopathy (PVR) tend to have a better prognosis after the treatment. On the other hand, uveitis, giant tears, breaks secondary to trauma, choroidal detachments and PVR tend to have a worse prognosis.[6]

Objectives

To evaluate the best evidence regarding the effectiveness and safety of interventions for the prevention and treatment of retinal detachment through the analysis of Cochrane reviews to resume the most appropriate conduct in the face of this pathology.

Methods

Design

This was a review of Cochrane reviews, a high standard of methodological design and implementation in systematic reviews (SR) about retinal detachment.

Criteria for including reviews

We only included the last version of completed Cochrane SR that evaluated the effects of different interventions for preventing or treating retinal detachment. The protocols of systematic reviews, empty review and withdrawn reviews were not considered.

Search for reviews

We carried an electronic search in the Cochrane Library (via Wiley) on June 08, 2020 as presented in table 1.

Table 1
Search strategy

#1 MeSH descriptor: [Retinal Detachment] explode all trees
#2 (Detachments, Retinal) or (Detachment, Retinal) or (Retinal Detachments) or (Retinal Pigment Epithelial Detachment)
#3 #1 or #2

Filters: in Cochrane Reviews; in Title, Abstract, Keywords

Selection of reviews

Two authors independently selected and evaluated all the systematic reviews retrieved, in order to confirm their eligibility in accordance with the inclusion criteria. Any divergences in the selection process were resolved by consensus.

Presentation of results

Were found four titles by search strategy and four[7-10] completed inclusion criteria, all addressing the therapeutic aspect of RD.

Results

We presented all the included SR in a qualitative synthesis. We summarized and presented the following characteristics: PICOs (population, intervention, comparator and outcomes), goals, methods, main findings and certainty of evidence in accordance with the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation).[11] A summary of each systematic review is presented narratively below. The table 2 presents the main findings.

Pneumatic retinopexy versus scleral buckle(7)

Pneumatic retinopexy[12] and scleral buckle (SB) are procedures indicated for RD, each one with indications and contraindications.[13] A study from 1997 to 2007 showed a decrease in SB as an alone procedure to 69% from 8691 to 2660 procedures and pneumatic retinopexy RD were relatively stable changing less than 25% in the same period.[14]

This SR showed two RCT (randomized clinical trials), 218 eyes, six-months follow-up and found adverse events:

Reattachment: fewer eyes in the pneumatic retinopexy group (risk ratio (RR) 0.89, 95% confidence interval (CI) 0.77 to 1.02, 218 eyes), but with uncertain results due to imprecision results.

Recurrence of RD: pneumatic retinopexy group were more likely to have had a recurrence of retinal detachment (RR 1.80, 95% CI 1.00 to 3.24, 218 eyes) but author related uncertain because of the lower confidence interval (CI).

Choroidal detachment: fewer cases in pneumatic retinopexy group (RR 0.17, 95% CI 0.05 to 0.57, 198 eyes).

Myopic equal to or greater than 1 diopter spherical equivalent: more susceptible in scleral buckle group (RR 0.04, 95% CI 0.01 to 0.13, 198 eyes).

Ocular adverse events: cataract (RR 0.92, 95% CI 0.06 to 14.54, 198 eyes), glaucoma (RR 0.31, 95% CI 0.03 to 2.91, 198 eyes), macular pucker (RR 0.74, 95% CI 0.20 to 2.67, 198 eyes), and proliferative vitreoretinopathy (RR 0.94, 95% CI 0.30 to 2.96, 218 eyes). No one was statistically significant and uncertain due to small numbers of events.

Not reported mean change in visual acuity, quality of life data, or economic measures.

Table 2
Summary of findings

Systematic review	Characteristics	Objective/ Intervention	Outcomes	Quality of evidence (GRADE)
Pneumatic retinopexy versus scleral buckle for repairing simple rhegmatogenous retinal detachments (7)	Published 2015 2 RCT (218 eyes of 216 participants)	To assess the effectiveness and safety of pneumatic retinopexy versus scleral buckle or pneumatic retinopexy versus a combination treatment of scleral buckle and vitrectomy for RRD.	Reattachment of the retina RR 0.89 (0.77 to 1.02) favorable to retinopexy.	Moderate
			Recurrence of retinal detachment RR 1.80 (1.00 to 3.24) in retinopexy group.	Moderate
			Any operative ocular adverse event RR 0.67 (0.32 to 1.42)	Low
Intravitreal low molecular weight heparin and 5-Fluorouracil for the prevention of proliferative vitreoretinopathy following retinal reattachment surgery (8)	Published 2013 2 RCTs 789 participants No metanalyses due to high heterogeneity	Intravitreal low molecular weight heparin (LMWH) alone or with 5-Fluorouracil (5-FU) versus placebo, as an adjunct in the prevention of PVR following retinal reattachment surgery.	LMWH with 5-FU versus placebo (RR: 0.48, 95% CI; 0.25 to 0.92; n= 174 patients) at high-risk of developing postoperative PVR.	Not related
			LMWH with 5-FU versus placebo in reducing PVR rates (RR:1.45, 95% CI 0.76 to 2.76; n= 615).	
Tamponade in surgery for retinal detachment associated with proliferative vitreoretinopathy (9)	Published 2020 4 RCT 601 participants	To assess the safety and effectiveness of tamponade agents used in surgery for RD complicated by proliferative vitreoretinopathy (PVR).	Silicone oil versus SF6: 2 years (1 RCT; 87 participants): VA ≥ 5/200: RR 1.57(0.93 to 2.66)	Low
			Silicone oil versus C3F8: 3 years (1RCT; 264 participants) VA ≥ 5/200: RR 0.97(0.73 to 1.31)	Low
			Standard versus heavy silicone oil:1 year (1RCT, 187 participants) Macular attachment: RR 1.00(0.86 to 1.15)	Low
			5000 versus 1000-centistoke (1RCT; 85 participants) 18months Retinal detachment: RR 0.89(0.54 to 1.48) RD after removed silicone oil: RR 0.36(0.08 to 1.67) IOP ≥ 21 mmHg: RR 0.90 (0.41 to 1.94) Cataract: RR 1.30 (0.89 to 1.89)	Low
Pars plana vitrectomy versus scleral buckling for repairing simple rhegmatogenous retinal detachments (10)	Published 2019 10 RCTs (1307 eyes of 1307 participants)	To assess the efficacy of PPV versus scleral buckling for the treatment of simple RRD	Primary retinal reattachment at 3 months: RR 1.07(0.98 to 1.16; 9 RCT; n=1261 participants)	Low
			Final anatomical success in 3 months: RR 1.01(0.99 to 1.04; 9RCT; 1235 participants)	Low
			Recurrence of retinal detachment: RR 0.75(0.59 to 0.96; 9 RCT; 1320 participants) favorable to PPV	Low
			Quality of life RR 6.22 (0.88 to 44.09)	Very Low

C3F8: perfluoropropane; RR: risk ratio; CI: confidence interval; 5-FU: 5-fluorouracil; IOP: intraocular pressure; LMWH: low molecular weight heparin; PVR: proliferative vitreoretinopathy; RCT: randomized clinical trial; RD: retinal detachment; SF6: sulfur hexafluoride; VA: visual acuity

Intravitreal low molecular weight heparin (LMWH) and 5-Fluorouracil[8]

Proliferative vitreoretinopathy (PVR) is a complication of RD and is a major cause of failure of retinal reattachment surgery. It could be treated with reattaching of RD but the visual outcome is very poor. Some studies show benefits with pharmacological interventions as retinoic acid[15-18], dexamethasone[19, 20], colchicines[21], paclitaxel (taxol)[22], daunorubicin[23] and 5-Fluorouracil (5-FU) with heparin[24, 25] to avoid this complication.

This SR found two RCT that did not meta-analyze due to heterogeneity between studies. One study found a beneficial effect of LMWH with 5-FU versus placebo (RR: 0.48, 95% confidence interval: 0.25 to 0.92; n= 174 patients) in reducing postoperative PVR compared to placebo and the other trial do not show a difference between LMWH with 5-FU versus placebo in reducing PVR rates (RR:1.45, 95% confidence interval: 0.76 to 2.76; n=615).

The author concluded that there is inconsistent evidence from two studies in patients with different risk of PVR on the effect of LMWH and 5-FU used during vitrectomy to prevent PVR.

Tamponade in surgery for RD with proliferative vitreoretinopathy[15]

Tamponade procedures in RD surgery are used to provide surface tension across retinal breaks, which prevents further fluid flow into the subretinal space until the retinopexy (photocoagulation or cryopexy) provides a permanent seal.[26] This can be achieved by the use of gases and silicone oil.[27]

SF6 versus silicone oil - in one year: SF6 present worse anatomic and visual outcomes (quantitative data not reported);

SF6 versus silicone oil - in two years: no evidence of a difference in visual acuity (33% versus 51%; risk ratio (RR) 1.57; 95%(CI) 0.93 to 2.66; 1 RCT, 87 participants; low-certainty evidence).

Silicone oil versus C3F8: no evidence of a difference in visual acuity (41% versus 39%; RR 0.97; 95% CI 0.73 to 1.31; 1 RCT, 264 participants; low-certainty evidence).

Standard versus heavy silicone oil: no evidence in VA at one year (mean difference -0.03 logMAR; 95% CI -0.35 to 0.29; 1 RCT; 93 participants; low-certainty evidence).

5000 versus 1000-centistoke: comparisons did not report data on visual acuity.

For macular attachment:

Silicone oil versus SF6 - in one year: favorable to silicone, quantitative data not reported.

Silicone oil versus SF6 - in two years: favorable to silicone, (58% versus 79%; RR 1.37; 95% CI 1.01 to 1.86; 1 RCT; 87 participants; low-certainty evidence).

Silicone oil versus C3F8 – in one year: no evidence of difference: (RR 1.00; 95% CI 0.86 to 1.15; 1 RCT, 264 participants; low-certainty evidence).

5000 versus 1000-centistoke: retinal reattachment was successful in 67 participants (78.8%) with first surgery and 79 participants (92.9%) with the second surgery, and no evidence of between-group difference (one RCT; 85 participants; low-certainty evidence).

Standard versus heavy silicone oil did not report on macular attachment.

Vitrectomy versus scleral buckling for rhegmatogenous retinal detachments[10]

Like any procedure, vitrectomy has its benefits and harms. Vitrectomy (PPV) performed with or without scleral buckling for repair of retinal detachment increased 78% during the period 1997 to 2007 from 11212 to 19923 procedures while SB alone decreased 69% from 8691 to 2660 procedures.[14]

Retinal reattachment at least three months after the operation: RR 1.07, 95% CI 0.98 to 1.16; 9 RCTs, 1261 participants, low-certainty evidence, no significant.

Postoperative visual acuity: no evidence of important difference between the groups: Mean difference (MD) 0.00 logMAR (95% CI -0.09 to 0.10, 6 RCTs, 1138 participants, low-certainty evidence).

Anatomical success: little or no difference between the groups: RR 1.01 (95% CI 0.99 to 1.04, 9 RCTs, 1235 participants, low-certainty evidence).

Redetachment: accused favorable with statistically significance in PPV group: RR 0.75 (95% CI 0.59 to 0.96, 9 RCTs, 1320 participants, low-certainty evidence).

Quality of life measured by "satisfied with vision": showed no significance but favorable to PPV: RR 6.22, 95% CI 0.88 to 44.09, 1 RCT, 32 participants.

All studies reported adverse effects; however, it is uncertain whether participants or number of adverse effects which bring bias for the analysis of results.

As the degree of evidence varies from low to very low, uncertainty as to outcome estimation persists and needs further study to benefit decision making.

Discussion

This review included four Cochrane SRs that evaluated three surgical techniques and one pharmacological intervention for RD, one of them did not assess the certainty of the body of evidence based on the GRADE[11] approach.

Additionally, the group of pneumatic retinopexy was less susceptible to choroidal detachment and myopic shift equal to or greater than 1 spherical diopter as adverse events when compared with scleral buckle. Although there is no statistically significant difference in visual acuity between standard and heavy silicone oil and between C3F8 and silicone oil, the following interventions may present some benefits for RD: (a) LMWH with 5-FU reduces the risk of developing postoperative PVR in a solitary trial without GRADE; (b) silicone oil was favorable for macular attachment at two years compared to SF6; (c) Retinal redetachment was reported in fewer participants in the PPV group compared to the scleral buckling group.

In summary, the pneumatic retinopexy uses gas bubble (air, SF6, C3F8), into posterior cavity through the pars plana to close the detached retina and increase the reabsorption of the subretinal fluid. The formally indications are: a single superior 8 clock-hours breaks or more than one break within 1-2 clock-hours without means opacity or proliferative chorioretinopathy (PVR) C or D. This technique depends on patient collaboration with head position during and after the procedure to bubble tamponades the breaks.[6] So, life quality should be assessed in all trials.

The scleral buckle procedure uses the external scleral indentation to approach the detached retina and the transscleral cryopexy to make the adhesion at the local breaks. In the approach the four rectus muscles are isolated and the silicone tire is passed with a band under them placed over the site of the break.[28]

The primary vitrectomy consists to remove the vitreous and the traction in the retinal breaks after the complete posterior vitreous separation; drain the subretinal fluid by retinotomy or by perfluorocarbon liquid technique; tamponade the breaks with gas (SF6, C3F8), air or silicon oil; and make the adhesion around

the breaks (laser or cryopexy). In addition, it can be associated with scleral buckle procedure.[5]

Pneumatic retinopexy is a less involved office procedure compared to vitrectomy or scleral buckle with very good results.[29] A recent RCT with 176 patients concluded that Pneumatic retinopexy should be considered the first-line treatment in patients fulfilling criteria for the management of primary RRD because it offers superior VA, less vertical metamorphopsia, and reduced morbidity when compared to PPV. In practice, we observe the specialist's affinity for pneumatics due to practicality and good results, ideally for a superior and single retinal break with less than or equal to one clock hour size and for collaborative patients.

We are experiencing a period of migration from SB surgery to PPV when the case has not a strong indication for a procedure, it is common to see attempts to convert from one procedure to another. For some ophthalmologists, this change occurred because vitrectomy is a safer, more controlled procedure and has experienced a period of an important evolution in equipment. Unlike scleral buckling, vitrectomy has evolved and does not involve the type of "blind" maneuvers that scleral buckling requires, such as external drainage of subretinal fluid. Besides, vitrectomy does not change the shape of the eye and does not induce myopia, diplopia, ischemia of the globe or choroidal hemorrhage.

Although the difference in primary success is minimal or does not exist between PPV and SB, the former resulted in more adverse events, such as new iatrogenic breaks and acceleration the development and progression of cataracts. Therefore, must be accurately indicated.[10] In addition, in phakic patients, SB seems to offer modest cost savings compared to PPV for the repair of RRD, whereas in pseudophakic and aphakic patients, PPV appears to be cheaper than SB.[30]

The advantages and disadvantages between PPV and SB are still quite controversial in the reviews. We still do not know whether PPV is more effective than scleral buckling at increasing primary reattachment rates and at improving postoperative visual acuity. When the chance of redetachment, this study found that in the PPV group, this chance would be greater. However, there are authors who claim that scleral buckling is associated with retinal redetachment more often compared to PPV,[10] while others believe that PPV and scleral buckling seem equally effective at reducing rates of recurrence of retinal detachment.[31] The probable cause for this discordance is the number of studies included.

Although controversy, asymptomatic breaks can also be treated as a way to prevent retinal detachment. The annual number of prophylaxis procedures for RD in the United States from 1997 to 2007 averaged between 16031 to 19437.[14] Treatment of asymptomatic lattice degeneration and management of incident acute PVD symptomatic offer a low cost and a favorable cost-utility (low $/QALY) as a result of the minimization of the cost and morbidity associated with the development of RD, thus justifying current practice standards.[32]

In this sample, we did not find RS that addressed DR prophylaxis such as laser for holes, degeneration, or in contralateral eyes for prevention. We found two empty Cochrane SR, one in prevention in lattice degeneration[2] and the other in giant tears,[33] showing that doubt remained in the literature. The fact that the review is empty reveals the lack of clinical trials in the literature. In a quick search of the literature, we find few RCT on prevention[34, 35] as well as some retrospective one.[36]

The major tamponade agents available today are various gases and silicone oils. The major advantage of gas tamponade is that the gas spontaneously dissipates, usually over several weeks, while silicone oil is permanent and may eventually require surgical removal. SF6 gas was associated with worse anatomic and visual outcomes than silicone oil, although some of these differences diminished after two years. Either silicone oil or C3F8 gas appeared to show comparable results for final visual acuities of 5/200 or better at one year and macular attachments at one year. Despite the many theoretical benefits of a heavier-than-water tamponade silicone oil agent in treating participants with inferior vitreoretinal pathology, no important advantages were reported in this study.[9]

This overview evaluated only the RS Cochrane, a high standard of execution, to support decision making and we can observe the lack of prophylaxis and the degree of evidence varying from moderate to very low in presented SR which means that still, new RCTs can change the current orientation or that it will very likely change.

Conclusion

The choice of approach used to retinal detachment treatment depends on each surgeon and each indication. However, this review noted pneumatic retinopexy tends to have fewer adverse events than scleral buckle. There are some benefits on LMWH with 5-FU use reducing postoperative PVR. and silicone oil has shown to be better compared to SF6 for macular attachment in 2 years. These points can be considered when choosing the technique to improve better results in cases of retinal detachment.

In addition, there is still a need for studies with a prophylactic RD approach in case of tearing and peripheral degeneration and studies with greater evidence of which surgical technique is most appropriate for each indication of RD considering the economic cost and the patient's quality of life.

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