Role of Bleb Needling in Rescuing Failing Blebs - A Review

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Abstract

Bleb failure is one of the common complications of trabeculectomy surgery. The treatment of failed bleb involves a second trabeculectomy procedure, an implant surgery or restarting the patient on medications. Bleb needling is a procedure that if done correctly, can revive a failing bleb and also negate the need to do a repeat procedure in a less interventional fashion. Hence, the knowledge of this procedure is essential for a clinician to manage cases of bleb failure that present routinely in outpatient department. This article entails various aspects of bleb needling procedure, its method, indications and literature review.

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Trabeculectomy is the most popular and commonly performed glaucoma surgery, especially in Asian countries. It has undergone substantial development from the time of its inception. Use of anti-fibrotic agents like mitomycin C have revolutionized the surgical outcome of trabeculectomy and has enhanced the success rate over the years. However, the bleb can sometimes succumb and fail after surgery owing to an exaggerated healing response. In these situations, the surgeon either has the choice of restarting the anti-glaucoma medications (AGM's), opting for a repeat trabeculectomy or choosing a glaucoma drainage implant (GDI) procedure. Restarting AGM's involves a negative impact on the quality of life and further increases the economic burden on the patient. A repeat trabeculectomy carries a lower chance of success than the initial procedure while a GDI procedure requires a specific skill and experience and comes with its own risks. So, before deciding for a more interventional procedure, it is reasonable to plan bleb needling for such patients since it is quicker, less interventional, can give time to the surgeon and can even negate the need for another surgery. In this article, we will review the various aspects of bleb needling with many related options along with their success rates, complications, and emerging trends.

Bleb needling is a procedure by which the fibrous tissue which forms in the subconjunctival and subscleral area due to excessive healing response following trabeculectomy is incised using a needle to maintain the patency of the entire pathway.

As the success of glaucoma filtration surgery is dependent on the wound healing response, it is imperative to know the natural process of wound healing.

Wound Healing in Glaucoma Surgery

During trabeculectomy, surgical trauma to the ocular tissues incites inflammation and scarring as a part of normal repair mechanism and healing response of the body. However, the outcome of the surgery is determined by the delicate balance between organized tissue repair and amount of disorganized scarring post- surgery.

There are three well-known stages of wound healing[1].

Stage of Inflammation

This stage starts immediately after surgery and peaks at 3-5 days. Apart from vasoconstriction of blood vessels and extracellular shift of proteins, there occurs inflammatory cell activation and secretion of tissue factors such as histamine, serotonin, prostaglandins, leukotrienes and complement factors. This leads to increased vascular permeability and accumulation of fibrinogen, fibronectin and platelets. Platelets attach to the fibrin network as well as vascular endothelial cells forming a temporary clot. Topical steroids given frequently in the early post-operative period help to control inflammation at this stage.

Stage of Fibroblast proliferation and stage of Collagen synthesis

There is a considerable overlap between these two phases. There is activation of macrophages (formed from monocytes) that cause fibroblast migration and proliferation leading to deposition of procollagen. This is eventually converted to collagen and stabilized by mucopolysaccharides. Angiogenesis and further fibroblast proliferation causes development of a granulation tissue bed. Vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and transforming growth factor beta (TGF beta) are all responsible for further continuation of the cycle.[2] However, anti VEGFs which are theoretically known to be antiangiogenic[3] were found to be less efficacious than MMC[4] on comparative study. More commonly, use of intra-operative and post -operative MMC[5] and 5-FU[6] have been found to down regulate fibroblast activation and collagen synthesis. Amniotic membrane graft (AMG) has also been tried and is shown to have beneficial effect on bleb survival.[7] However till now there is no firm evidence to suggest its consistent and routine use in trabeculectomy.

Stage of Remodelling

This is a stage of organization and reorientation of collagen fibres and can prolong until six months to a year after surgery leading to secondary changes in the bleb characteristics. Ologen, a recently developed biodegradable material is theorized to alter the stage of remodelling but relevant

studies have not shown a significant success rate when compared with MMC.[8]

Indications

Bleb needling is indicated in various types of non-functional or dysfunctional blebs.

Features of an Ideal Functional Bleb (Figure 1): A functioning bleb should be low lying, diffuse with mild vascularity (similar to the normal conjunctiva) and posterior in area and location. The wall should be thick walled but translucent with a large number of micro-cysts. The micro-cysts however are usually seen only on anterior segment OCT (ASOCT) and other imaging modalities and may not be visible on slit lamp examination. The anterior chamber (AC) is well formed with a patent sclerostomy and intraocular pressure (IOP) maintained in low teens.

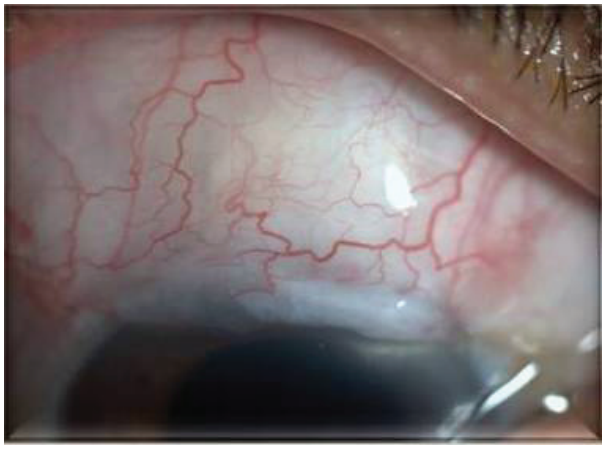

Figure 1: *An ideal functional bleb*

Types of Non Functioning Bleb

1) On the basis of bleb morphology

a) **Early failing bleb** (Figure 2): It is caused by excessive fibroblastic proliferation in the early post operative period (within 2 weeks) leading to scarring at conjunctival and subconjunctival interface. It is characterized by a flat bleb with excessive vascularity over the surface. Intraocular pressure is high despite a patent sclerostomy. Bleb rise does not occur even with massage.

Figure 2: *An early failing bleb*

b) **Encapsulated or encysted bleb** (Figure 3): It is caused by excessive collagen synthesis and occurs within 2-4 weeks. It is characterized by high IOP and a deep AC. The bleb is tense, elevated and thick-walled with large vessels coursing over it along with intervening avascular areas. There will be an absence of micro-cysts.

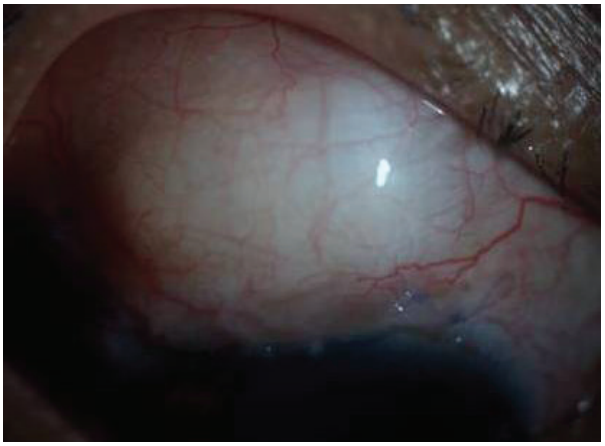

Figure 3: *An encapsulated bleb*

c) **Late failing/failed bleb**: It is caused by secondary changes in bleb characteristics due to remodelling that occurs 3-6 months after surgery. Scarring occurs at the sub-conjunctival and episcleral interface. The condition is associated with high IOP, a well-formed anterior chamber and a flat fibrosed thick walled bleb with minimal vascularity.

2) On the basis of time duration

a) **Early bleb failure**: It occurs within one month. Common causes are internal blockage of sclerostomy that goes unattended, excessive inflammation or a tight scleral flap preventing filtration. Early bleb failure can also be caused by bleb leakage in the immediate postoperative period. The anterior direction of aqueous filtration causes the posterior part of the bleb to undergo early fibrosis.

b) **Late bleb failure**: It presents after one month and occurs usually due to subconjunctival and episcleral fibrosis.

Plan of Management for Failing/Failed Bleb

Early bleb failure

A frequent follow up after trabeculectomy is very important to help in recognition of any bleb-related complication like early bleb leak/early bleb fibrosis. An increasing IOP over the initial few days/weeks should make the surgeon alert to early bleb failure and look for the cause to take appropriate measures; otherwise, it is difficult to reverse the process of fibrosis. In the early postoperative period, if a patient presents with a flat bleb, high IOP and deep AC, the first reflex should be to perform a careful gonioscopy to rule out a blockage of the sclerostomy site. If the sclerostomy is found to be blocked by blood clot and/or fibrin which is commonly seen in the early postoperative period, gentle bleb massage and increasing topical steroids generally suffices to either

dislodge/dissolve the clot/fibrin. However, in case of blockage caused by vitreous, Nd: YAG laser may be required to break the blockage.

Even in cases where the sclerostomy is patent but the IOP is high, gentle digital massage should be done. This manoeuvre forces aqueous through the opening and the bleb begins to rise and start functioning. The patient can then be called at frequent visits to assess the status and functioning of the bleb. The patient or the attendant can be taught the method of bleb massage at home till laser suturolysis or removal of releasable suture can be safely performed.

If repeat massages are not successful, removal of the releasable suture or Argon Laser Suturolysis of fixed scleral flap sutures can be done. These manoeuvres can be safely done after around 10 days of the surgery. They are very helpful in the early phase of bleb failure but may not help in the management of late bleb failure due to organized fibrosis.

If IOP still remains high despite all the above conservative measures, a diagnosis of failing/failed bleb is made and needling procedure can be undertaken.

Figure 4a: *Needling procedure*

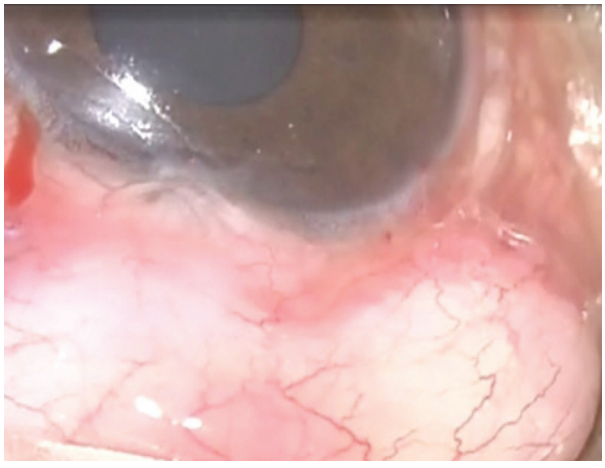

Figure 4b: *Elevated bleb at the end of needling procedure*

Principle: Needling is done to incise and break the fibrotic adhesions that surround the bleb subconjunctivally and cause resistance to the aqueous outflow. This re-establishes the pathway from anterior chamber to subconjunctival space thereby lowering the IOP. A number of agents can be injected or applied sub- or transconjunctivally to increase the success rate of the procedure. (Figure 4a- bleb needling 4b- formation of bleb during needling process)

Literature Review

Revision of filtering blebs started as early as 1941 when Ferrer performed conjunctival dialysis in which he used a spatula to separate conjunctival adhesions from sclera.[9] Pederson and Smith in 1985 first coined the term needling of blebs and reported a success rate of 69%.[10] However, many patients in their study required medications in the post operative period.

Use of anti-fibrotic agents with needling

5 Fluorouracil

Repeated 5-FU injection is commonly employed with bleb needling procedures. It is also used in high-risk cases with early signs of bleb failure such as rising IOP on subsequent visits, moderate to severe vascularisation and low lying blebs. 5-FU which is a halogenated pyrimidine analogue acts by selectively inhibiting DNA synthesis by blocking the enzyme hyonidylate synthetase. This is responsible for the cytotoxic action of the drug leading to arrest of cells in DNA synthesis stage. Hence it acts only on actively dividing cells. The subconjunctival dose used is 5mg in 0.1ml.

The efficacy of 5-FU as a bleb needling agent in failing/failed bleb has been demonstrated in various studies. It was Ewing and Stamper (1990) who first used 5-FU in the postoperative period following needling.[11] They had a success rate of 91.6%, out of which 63.6% required post needling medication. Shin et al[12] first administered 5-FU during needling and achieved a success rate of 80%. However, more than 60% required medications postoperatively. The success rate was higher in cases with late failed blebs. Broadway et al attained a success rate of 60% with the use of 5-FU in a median follow up of 18 months.[13] They reported a success rate of 47% for encapsulated blebs and 55% for flat blebs. Rochford and King in 2008 found a success rate of almost 60% in less than 2 years follow up and concluded that needling with 5FU is a viable option for short and intermediate term (< 3 months).[14] Their success rate was much higher for encapsulated blebs compared to flat blebs. So 5-FU definitely enhances success rate of the bleb needling procedure. However, patients may require AGM after the procedure.

Mitomycin C

Mitomycin is an antineoplastic/antibiotic agent that is derived from the soil bacterium Streptomyces caespitosus. It is an antimetabolite with an antiproliferative effect. It blocks DNA, RNA and protein synthesis thereby blocking all stages of cell cycle. It inhibits both dividing and resting cells. During needling, MMC can be given either in form of sponge application (Transconjunctival MMC) or subconjunctival injection.

Transconjunctival MMC

Transconjunctival MMC has been tried since last two decades and may enhance the success of the needling procedure in failing filtering blebs. Iwach et al, in 2003 for the first time reported the efficacy of MMC application after

needling procedure.[15] In this method, after a routine needling procedure, MMC in a dose of 0.5mg/ml was applied by means of a sponge left in contact with conjunctival epithelium for 6 minutes. Postoperatively, 63% of the patients received 5- FU injections. A success rate of 76% at 1 year and 72 % at 2 years was achieved. The failure rate was higher in only MMC group compared to combined MMC and 5-FU group (44% vs. 23%). Authors also found significantly higher chances of success with diffuse blebs (53%) compared to encapsulated blebs (19%) on comparison between types of dysfunctional blebs.

Needling with subconjunctival MMC

Mardelli et al used .01ml of MMC (0.4 mg/ml) and .02ml of Bupivacaine mixed with epinephrine (1 in 100000) subconjunctivally to revive failed filtering blebs. This was followed by needling 20 to 30min later.[16] The overall success rate was 76% in 1 year, but 42% cases required re-needling. A positive correlation was seen with race (whites) and past filtration surgery of over 4 years. Bielak et al in 2016 reviewed long-term efficacy of this procedure and achieved a success rate of 84% at 1 year which was maintained at 71% at 5 years. They concluded that late bleb needling (>6 months) had better chances of success than early intervention and recommended an interval of at least 6 months to allow healing of the bleb.[17] Pathak and Chaudhary, found comparable results in their 20 months follow up (84% success rate).[18]

Sub-conjunctival 5-FU vs. Sub-conjunctival MMC

Both these antimetabolites are effective in rescuing failing filtering blebs but having a broader and varied duration of action than 5-FU, MMC is found to be more effective and successful. Anand and Khan compared 5-FU and MMC in terms of long-term efficacy and safety in failed trabeculectomy eyes.[19] Results showed a higher number of needle revisions in the 5-FU group. The probability of IOP control was better in MMC group (71% vs. 45% at 1 year) compared to 5-FU group. Fifty percent of the eyes that failed with 5-FU, underwent successful needling with MMC and maintained normal IOP till 2 years of follow up. There was no significant difference in complication rates in two groups. A recent study comparing the two anti- metabolites showed almost equal IOP reduction post needling, but the overall success rate at 12 months was higher in MMC group (75% vs. 60%).[20] The authors have concluded that the ideal time to perform needling is during the cellular phase when the healing process can be modulated.

Other anti proliferative agents

Intra-bleb triamcinolone acetonide:

Tham et al. (2006) reported use of 0.03 ml (40mg/ml) of triamcinolone acetonide (TA) at the end of needling procedure. There was a significant reduction in IOP by around 50% along with a reduction of the mean number of topical drops.[21] The only complication was persistent TA deposits which had no further additional consequences. Authors concluded that intra-bleb TA was safe and effective up to 3 months after surgery. However, in other studies, TA was found to be less efficacious than MMC and did not increase the long-term success rate of surgery.[22]

Bevacizumab (Avastin):

The production of vascular endothelial growth factor (VEGF) increases after filtration surgery and its levels are up regulated in aqueous. Anti VEGFs influences scar tissue formation by reduction of cytokine release and fibroblast formation.[23,24] Adopting this rationale, there were several studies conducted to determine the effect of Anti VEGF post-trabeculectomy. However, it was not established to be very effective in preventing failure.[25]

Complications of needling

Needling may be associated with minor complications like sub conjunctival hemorrhage (most common), leak from needling site, over filtration, hyphema and epithelial defect. Major complications can occur secondary to shallow AC and low IOP such as choroidal detachment, hypotonic maculopathy, and corneal decompensation.[14-20]

Prediction of risk factors for failure of needling:

Yan and Lam investigated the predictive factors for failure of needling with MMC following trabeculectomy.[26] They observed 114 cases of needling with MMC (0.3mg/ml) for 12 months. The study found non-Caucasian race, more than one trabeculectomy, history of previous needling, pre needling IOP >25mmHg, post needling IOP >12mmHg and resumption of glaucoma medications following needling being correlated with needling failure. Factors not correlating to needling failure included: gender, age > 65 years, pseudophakia, post-operative time from surgery > 6 months, diabetes, post-op laser suture lysis and the number of glaucoma medications before needling.

Conclusion

Needling is a safe and effective low-cost procedure that has the potential to rescue failing filtering blebs. It can be tried in practically all cases of bleb failure owing to extra ocular obstruction before subjecting the patient to a more interventional procedure. As the literature review shows, needling with MMC injection enhances the success rate of the procedure and is a better alternative to 5- FU. Long-term success rates are unknown and prospective studies with a longer follow up might provide more insights into the long-term safety and efficacy of the procedure.

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