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Update on Nonpenetrating Glaucoma Surgery

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Over the last 30 years, trabeculectomy has been the standard of care for surgically-managed glaucoma. Several refinements in surgical technique and postoperative care (eg, the use of antimetabolites, argon suture lysis, and releasable sutures) have improved the success rates for trabeculectomy, but complications continue to occur at significant rates. In the short-term, these complications include hypotony with or without maculopathy, shallowing of the anterior chamber, choroidal effusions or hemorrhages, hyphema, and cataract formation. Long-term complications are often associated with bleb morphology, resulting in late bleb leakage that can potentiate blebitis and endophthalmitis.

Although initially proposed in the 1950s, nonpenetrating glaucoma surgery (NPGS) only emerged in the 1990s as a surgical alternative to standard trabeculectomy. The promise of NPGS, according to its proponents, is an increased safety profile with equal efficacy in lowering intraocular pressure (IOP) as standard trabeculectomy. In the absence of a full-thickness sclerotomy, the additional filtration that occurs with NPGS takes place across semi-permeable ocular structures, thus maintaining some resistance to outflow and resulting in a greatly reduced incidence of overfiltration and hypotony. The maintenance of aqueous flow and avoidance of early hypotony increase the long-term likelihood of successful IOP lowering. Furthermore, because there is no penetration into the anterior chamber, sudden decompression and associated complications, as well as intraocular inflammation, hyphema, and infection, are significantly reduced. Blebs resulting from a nonpenetrating approach are typically diffuse and low-lying as opposed to blebs associated with trabeculectomy that can be cystic and avascular, and thus prone to leakage and infection.

Currently, 2 NPGS procedures are described: deep sclerectomy (DS) and viscocanulostomy (VC). This issue of *Ophthalmology Rounds* reviews the history, mechanisms of action, technique, and literature supporting the use of NPGS as a surgical intervention for the treatment of glaucoma.

History

The first description of NPGS came from Epstein who documented the percolation of fluid through intact corneal tissue when deeply excising pterygia in the paralimbal region.[1] He proposed a paralimbal DS, in which a narrow band of scleral tissue was removed over Schlemm's canal (SC) for 180°. In 1968, Krasnov proposed a similar procedure; he incised SC and then removed a band of sclera for 120°.[2] The long-term success of these procedures was poor, secondary to the direct apposition of conjunctiva against the exposed trabecular meshwork. After the simultaneous introduction of standard trabeculectomy by Sugar and Cairns in the late 1960s,[3,4] the technique was abandoned and further refinements in NPGS were arrested until the1980s, when it was recognized that NPGS could be performed under a scleral flap, thus precluding conjunctival scarring and resulting in significantly improved longevity of filtration.[5,6]

Patient selection

Generally, NPGS is indicated in any patient with open-angle glaucoma who is being considered for standard trabeculectomy. Specific indications to perform NPGS are derived from clinical scenarios in which there is a high risk of an adverse event occurring with standard trabeculectomy, as outlined below and in Table 1.

Due to associated complications, standard trabeculectomy is generally indicated only when a patient has failed maximum tolerated medical therapy. Unfortunately, multiple topical agent usage is associated with low-grade conjunctival inflammation and scarring that reduces the long-term efficacy of the surgery.[7] The superior safety profile of NPGS over standard trabeculectomy makes surgical intervention a reasonable option before exhausting all medical options.

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Table 1: Patient Selection

Indications

All open-angle glaucomas (especially if)
- Early surgical intervention required
- Monocular patient
- Large diurnal fluctuations
  - Pigment dispersion glaucoma
  - Pseudo exfoliation glaucoma
- High risk of choroidal effusions or hemorrhages
  - Axial myopia
  - Hypertension
  - Previously vitrectomized eye
  - Atherosclerosis
  - History of choroidal effusion or hemorrhage
  - Increased episcleral venous pressure
  - High risk of postoperative hypotony
  - Young patients
  - High myopes
  - Males
- Uveitic glaucoma without extensive PAS
- Young patients

Contraindications
- Trabecular meshwork obstructed
  - Extensive synecial angle closure
  - Neovascular glaucoma
  - Occludable angles[1]
- Altered anatomy
  - Thin sclera
  - Significant limbal scarring
    - ◆ Previous scleral tunnel
    - ◆ Previous extracapsular cataract extraction

[1] NPGS can be combined with cataract surgery or peripheral iridotomy
PAS = peripheral anterior synechiae

Particular consideration should be given in conditions that are associated with large diurnal IOP variations, like pigment dispersion syndrome and pseudo-exfoliation syndrome. In these cases, surgical intervention may be superior to medical management in controlling IOP fluctuations.[8-11] Furthermore, NPGS, particularly VC, is less dependent on the relative health of the conjunctiva.

NPGS avoids sudden decompression of the eye and is particularly indicated in patients with a high risk of choroidal effusion or hemorrhage should they undergo standard trabeculectomy, especially if the patient is monocular. NPGS is also preferred in patients at risk of postoperative hypotony.

The absence of penetration into the anterior chamber reduces the amount of postoperative inflammation, thus reducing the risk of postoperative cataract formation. This is particularly beneficial for young patients. Furthermore, bleb morphology associated with NPGS (ie, absent in VC or "low-lying" in SC) allows for continued contact lens wear post-operatively and theoretically reduces the long-term risk of blebitis and contact lens-related bleb problems.

NPGS is generally contraindicated in eyes, in which the trabecular meshwork has been obstructed or damaged, or when there are structural abnormalities and anomalies in the limbal and paralimbal regions. Of note, argon laser trabeculoplasty and selective laser trabeculoplasty are not contraindications to NPGS.

Technique

Most of the instruments required to perform NPGS are found in a standard trabeculectomy set; however, the use of diamond blades and other specialized equipment facilitate the performance of the surgery.

NPGS can be performed under local (authors' preference), peribulbar, or retrobulbar anesthesia. After the application of anesthetic, a fornix-based flap is created in the superior temporal or nasal quadrant. After undermining surrounding conjunctiva and achieving hemostasis, a superficial scleral flap is created at a depth of 33% to 50% scleral thickness. In DS, the flap is 5 mm x 5 mm square whereas, in VC, it is a parabolic flap that enhances the watertight closure. In both cases, the flap is carried 1 to 2 mm into clear cornea.

The next step is creation of a deeper flap at 90% of the scleral thickness. This represents the most technically challenging step in NPGS and should be performed under high magnification. With the DS procedure, this flap comprises a 4 mm x 4 mm square; with VC, it is again parabolic. At the correct depth, the irregular arrangement of the scleral fibers and the deep purple hue of the choroids are clearly visible. At this depth, advancing the flap anteriorly, the scleral fibers in the base change from a random arrangement to an organized arrangement circumferential to the limbus; this represents the scleral spur that is just posterior to the SC. Continuing the dissection forward at this level will "unroof" the SC, beyond which is a natural plane between Descemet's membrane (DM) and the overlying stroma. At this point, little, if any force, is required to advance. The dissection must continue at least 1 mm into clear cornea to create an adequate trabeculo Descemet's membrane (TDM). Vertical relaxing incisions are required at the lateral edges of the flap to carry the flap into the cornea. Figure 1 illustrates the anatomy of the dissection. During this step, great care must be taken not to rupture DM, which is susceptible to inadvertent traumatic perforation. The flap must then be carefully removed and, in doing so, the surgeon will notice the percolation of fluid through the TDM. At this point, the two NPGS procedures diverge.

- **In VC,** a paracentesis is performed to create a mild degree of hypotony so that blood is refluxed from SC, thereby allowing localization of the cut ends. SC is then intubated with Grieshaber cannula and high-viscosity viscoelastic material is injected 5-6 times into each cut end – widening the SC and thus improving flow through SC. The superficial flap is then reflected back into place and sewn tightly. Finally, the high-viscosity viscoelastic is injected underneath the flap to maintain the scleral lake. High-viscoscity viscoelastics have been shown to prevent fibrinogen migration, thus minimizing scar formation that could obliterate the scleral lake over time. The conjunctiva is then closed in the usual fashion

- **In DS,** after the removal of the deeper scleral flap, the inner wall of SC is peeled (Figure 1), at which time, the surgeon will notice an immediate increase in the percolation of fluid through the TDM. A space-occupying device, usually a collagen implant (author's preference), is placed centripetally in the cavity formed when excising the deeper flap in order to maintain the scleral lake. It is sewn in place using a single 10-0 nylon suture (Figure 2). The superficial flap is then loosely closed using two 10-0 nylon sutures to promote bleb formation. The conjunctiva is then closed in the usual fashion.

In addition to the use of space-maintaining devices, mitomycin C (MMC) has been used as an adjunctive ther-

Figure 1: At the correct depth, advancing the flap anteriorly, the scleral fibers in the dissection bed change from a random arrangement to an organized arrangement circumferential to the limbus; this is visible by the glistening white scleral spur just posterior to Schlemm's canal (SC). Continuing the dissection forward at this level will unroof SC, beyond which is a natural plane between Descemet's membrane (DM) and the overlying stroma requiring little, if no force to advance. Note the peeling of the inner wall of SC in the figure.

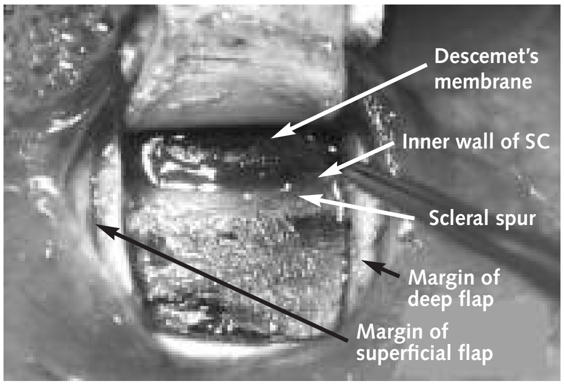
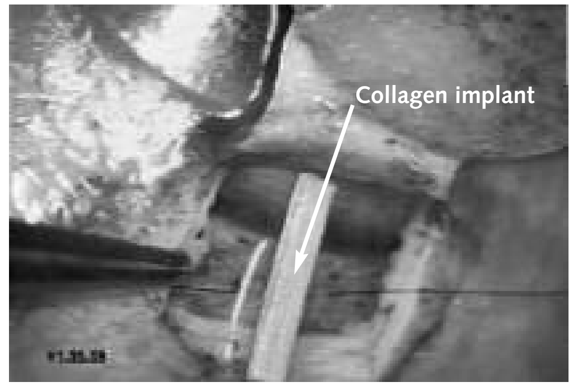


Figure 2: To fixate the collagen implant to maintain the scleral lake, a 10-0 nylon suture is placed in the scleral bed. This suture is passed full thickness through the remaining sclera, but remains in the suprachoroidal space. Collagen implants have also been shown to reduce inflammation adjacent to the scleral flap and bleb by activating collagenase.



apy intra-operatively, as well as postoperatively. Other adjunctive therapies include 5-fluorouracil and Nd:YAG goniopuncture. The latter involves the application of Nd:YAG laser to the TDM with the use of a goniopuncture, thereby creating micro-perforations and increasing filtration. The role of these adjunctive therapies, as well as that of NPGS, as a viable surgical entity is discussed below.

Mechanism of action

The mechanism of action behind IOP lowering is clear in standard trabeculectomy – filtration occurs through a penetrating wound and underneath a partial thickness scleral flap. From here, aqueous flows into the subconjunctival space and is drained from the eye by the conjunctival tissues. In contrast, there is debate about how IOP is reduced with NGPS: first, where does the filtration take place and, secondly, where does the aqueous drainage occur?

With respect to filtration, Grant demonstrated that 75% of outflow resistance exists at the juxtacanalicular trabecular meshwork (JCTM), which is also where altered resistance exists in primary open-angle glaucoma.[12,13] During NPGS, many surgeons remove the inner wall of SC and it is thought that this also removes the juxtacanalicular connective tissue (JCT) in that region. Some argue that this is the principal mechanism of filtration in NPGS, which is clinically correlated with increased percolation of aqueous noted after peeling the inner wall of SC intraoperatively. Others have argued that microperforations that enable aqueous to pass are created in the TDM during surgical dissection of the deeper sclerocorneal flap and peeling of the inner wall of SC.[14-16] The physiologic repair of the microperforations is thought to increase resistance to outflow and account for increased IOP observed over time postoperatively.[17,18] Finally, it has been postulated that filtration occurs through the TDM; this is analogous to fluid movement through a semi-permeable membrane. Experimental studies in rabbits have demonstrated that the TDM has a limited ability to function in this manner; however, the effect is likely more significant in humans, in whom the TDM is thinner.[19,20]

Aqueous drainage is proposed to occur via a variety of mechanisms in NPGS. With DS, the superficial scleral flap is sewn loosely to the adjacent sclera to allow aqueous to seep from the scleral lake to the subconjunctival space, resulting in the formation of a bleb. In addition, ultrasound biomicroscopy studies have demonstrated hypoechoic areas in the supraciliary area deep in the aqueous lake, as well as in the adjacent sclera.[21,22] This suggests that aqueous drainage also occurs via uveoscleral and transscleral pathways, respectively.[21] The additional drainage that occurs through these secondary pathways is likely the reason why DS produces blebs that are lower than those produced during standard trabeculectomy, despite comparable IOP lowering.[23]

In contrast to DS, in VC, the superficial scleral flap is securely sutured to the surrounding sclera, producing a water-tight closure. In addition to the uveoscleral and transscleral routes, drainage occurs through a mechanically altered SC.[24] The injection of a high-viscosity viscoelastic material into the cut ends of SC results in the dilation of the canal and creation of multiple microruptures in the inner and outer endothelial walls.[16] The combined result is an increased capacity of SC and an associated lowering of IOP.

Review of the literature

The evaluation of a novel surgical technique requires evaluation of both the efficacy and safety of the procedure. A review of 35 major studies reporting on both of these parameters with respect to NPGS is presented in the following paragraphs.[17,23,25-58]

The first landmark study on NPGS was reported by Stegmann in 1999.[57] He reported on a consecutive series of 214 patients undergoing VC; mean IOP was reduced from 47.4 to 16.9 mm Hg and the success rates were 82.7% and 89% (for "complete" and "qualified" success, respectively). However, other early NPGS studies that primarily evaluated VC or DS without an implant, failed to demonstrate similar IOP lowering; and studies comparing NPGS to trabeculectomy suggested lesser efficacy in lowering IOP. In a prospective randomized controlled trial (RCT) of trabeculectomy versus VC, Jonsecu-Cuypers et al reported a 0% success rate with VC versus a 50% success with trabeculectomy at 6 months.[54] In another RCT comparing VC to MMC trabeculectomy, O'Brart et al reported a 24% versus 68% complete success rate for VC and MMC trabeculectomy, respectively.[50] However, in both of these studies, as well as many of the other early ones, Nd:YAG goniopuncture was either disallowed or, if required, was considered to indicate a failure of surgery because it effectively converts NPGS into a penetrating procedure.

Proponents of NPGS have countered that the need for postoperative modulation of flow with goniopuncture is no different from the need to perform argon suture lysis which, although it effectively converts a guarded procedure to full-thickness procedure, is not associated with the same risks as a full-thickness procedure. When 5-fluorouracil and goniopuncture were used as indicated, Shaarawy reported a 60% and 90%, complete and qualified success rate, respectively, at 34 months of follow-up.[45] Choosing an arbitrary mean final IOP of <15 mm Hg, 15 of 19 studies that excluded goniopuncture as an acceptable postoperative adjunctive treatment failed to achieve this mark, while 3 of 4 studies that did include goniopuncture, reported a final mean IOP of <16 mm Hg.

The first trial reporting on DS, by Mermoud et al, was a prospective study; it compared DS with a collagen implant to trabeculectomy.[17] There were 44 eyes in each group. At 24 months, complete success (<21 mm Hg) rates were 69% and 57% for DS and trabeculectomy, respectively, a difference that was found to be just significant (p=0.047). In a similar study, Cillino et al reported a 53% and 57% success rate (<21 mm Hg) for DS and trabeculectomy, respectively, at 24 months. Of note, Cillino et al did not utilize adjunctive techniques (ie, collagen implant and goniopuncture) with DS that were used in the former study.[32]

DS has generally proven to be more effective than VC in lowering IOP. As mentioned previously, of the 19 VC studies reviewed, only 3 (16%) achieved a final mean IOP of <16 mm Hg, while 9 of the 26 (35%) studies reporting on DS were able to achieve this mark. However, the use of adjunctive modalities with DS is crucial in lowering IOP. This is also the case for trabeculectomy, as is illustrated by the 2 studies presented above. Use of antimetabolites, either intraoperatively or postoperatively, has been proven to further reduce IOP in DS. In an RCT examining DS versus DS with MMC (40 patients in each group), Kozobolis et al reported a complete (qualified) success rate in 43 (50%) and 73 (90%) for DS and DS with MMC, respectively.[48] Overall, of the 7 studies reporting on DS without antimetabolites, none achieved a final mean IOP of <16 mmHg, in contrast to 9 of the 19 studies that did utilize antimetabolites.

The role of a space-maintaining device is equally important. Shaarawy and Mermoud reported on a RCT comparing DS with DS with collagen implant.[34] At 48 months, complete (qualified) success was reported to be 38 (69)% and 69 (100%) for DS and DS with collagen implant, respectively. Compiling the results of the 26 studies, only 2 of the 13 studies that did not use a space-maintaining device achieved a final mean IOP of <16 mmHg, while 7 of 13 studies that did utilize a device achieved this mark.

Although no trial has been designed to specifically decipher the effectiveness of goniopuncture, it is certainly clear – as was demonstrated with VC – that goniopuncture is an important adjunctive modality to be utilized with DS. Reviewing the 26 studies, none of the 7 that disallowed goniopuncture achieved a mean final IOP of <16 mm Hg, whereas 9 of the 19 studies that employed goniopuncture, when indicated, achieved this mark.

While there is not universal agreement on the efficacy of NPGS, the superior safety profile conferred by NPGS as compared to trabeculectomy is clear. Table 2 presents the mean complication rates for trabeculectomy, VC, and DS in the 35 studies reviewed. The authors have recently completed a randomized, prospective trial comparing trabeculectomy and DS with adjunctive therapy (namely antimetabolites, goniopuncture, needlings, and laser suture lysis) used as indicated. It demonstrated equivocal IOP lowering in each group, with a significantly superior safety profile in the DS group.

Conclusion

Early NPGS studies, primarily evaluating VC or DS without an implant, suggest that there is less efficacy with these procedures in lowering IOP when compared to MMC trabeculectomy. However, refinements to technique (eg, space-maintaining devices, antimetabolite use, and postoperative modulation with Nd:YAG goniopuncture) have resulted in comparable, if not superior, IOP lowering, while maintaining an excellent safety profile, particularly in DS with collagen implant. The IOP-lowering efficacy of VC is probably not as great as with DS with an implant. Currently, long-term data on NPGS is evolving. This suggests that the altered bleb morphology achieved with NPGS (shallow and diffuse in DS, and

Table 2: A meta-snalysis of the frequency (in %) of adverse outcomes from 38 studies

	Hyphema	Hypotony	Flat/shallow	Choroidal (effusion/hemorrhage)	Surgically-induced cataract	Late cataract progression
Trabeculectomy	17.21	14.15	16.67	13.89	8.00	12.89
Viscocanulostomy	13.16	5.86	4.63	3.47	1.00	4.50
Deep sclerectomy	8.77	2.84	0.86	3.73	0.00	9.63

non-existent in VC) reduces the risk for late leakage, blebitis, and endophthalmitis.

The knowledge gained from studying NPGS has been instrumental in furthering our understanding of the anatomy of the angle, as well as the importance of the choroids as a site of aqueous drainage. Whether NPGS represents the future of glaucoma surgery remains to be seen since multiple new glaucoma procedures and implants have recently been developed. The impetus for this intensive research and development is clearly the unfavourable adverse event rates associated with trabeculectomy and antimetabolites. Trabeculectomy has been used to surgically manage glaucoma for almost 40 years; however, now it is quite plausible and likely that MMC trabeculectomy will be reduced to a historical relic during the next decade.

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Upcoming International Meetings

25-28 May 2006
Third International Congress of Glaucoma Surgery
Toronto, Ontario
CONTACT: www.icgs2006.com

21-24 June 2006
Canadian Ophthalmology Society (COS)
Annual Meeting and Exhibition
Westin Harbour Castle, Toronto, Ontario
CONTACT: Ms Kim Ross
Email: kross@eyesite.ca
Website: www.eyesite.ca/annualmeeting/2006/

University of Toronto Department of Ophthalmology and Vision Sciences

Upcoming events

May 18, 2006	TOS/U of T VPP rounds Vaughan Estates
May 25, 2006	**VPP** – Dr. Shaun Singer Quality Assurance
June 9, 2006	Departmental Research Day
Oct. 14, 2006	International Neuroprotection meeting Contact: Dr. Neeru Gupta 416-864-5444

Note: This year's (September 2005 to May 2006) VPP rounds will be held at:
The Hospital for Sick Children
555 University Avenue, Toronto
Main Auditorium, Elm Wing, 1st Floor, Room 1246,
5:30 PM – 7:30 PM.

Change of address notices and requests for subscriptions for *Ophthalmology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Ophthalmology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

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