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Systematic overview of the efficacy of nonpenetrating glaucoma surgery in the treatment of open angle glaucoma

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Summary

Background: To evaluate the intraocular pressure (IOP)-lowering effects achieved by nonpenetrating glaucoma surgery (NPGS) and its modifications in patients with open angle glaucoma.

Material/Methods: Randomized controlled trials evaluating patients with primary and secondary open angle glaucoma treated with NPGS were identified through systematic searches. The main outcome measures were the percentage IOP reduction and the complete success rate. Complete success was defined as target endpoint IOP (usually less than 21 mm Hg) without medications. The pooled estimates were calculated using the random effects model.

Results: Both deep sclerectomy (DS) and viscocanalostomy (VCO) were less effective than trabeculectomy (TE) in lowering IOP, with the percentage IOP reductions at 2 years being 35.2% for DS, 30.2% for VCO, and 45.6% for TE. Intraoperative use of implants and mitomycin C (MMC) increased IOP-lowering effects of DS, with IOP reductions at 2 years of 41.1% and 41.7%, respectively. The complete success rates at 4 years were 35.4% for DS, and 22.7% for VCO, lower than that of TE (47.6%). The complete success rates of DS with implants and MMC of 64.6% and 52.1%, respectively, at 4 years, were greater than that of primary DS. NPGS caused major complications in fewer patients than did TE.

Conclusions: Primary deep sclerectomy and primary viscocanalostomy, which can significantly lower IOP, were associated with fewer complications than was TE. However, the IOP-lowering effects of both NPGS seem to be lower than that of primary TE. The efficacy of DS can be improved with the intraoperative use of implants and MMC.

key words: **nonpenetrating glaucoma surgery • open angle glaucoma • mitomycin C • implant • meta-analysis**

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Background

Trabeculectomy remains the standard surgical procedure used to treat open angle glaucoma; however, it is commonly associated with complications such as hypotony and cataract progression. Nonpenetrating glaucoma surgeries (NPGS) has been developed in recent years in order to improve its safety over that of the classical trabeculectomy [1]. The avoidance of overfiltration and hypotony has been the most important reason for the interest in NPGS. However, there have been intense discussions on the efficacy and longevity of NPGS, and the potential of NPGS to achieve target intraocular pressure (IOP) seems to be lower than in conventional trabeculectomy [2,3].

To facilitate IOP-lowering efficacy, numerous modifications of NPGS have been introduced, including deep sclerectomy and viscocanalostomy. Several implants and antimetabolites have also been applied. The diversity of the surgical procedures has made it difficult to draw conclusions that could be applied in clinical practice. Recently, several meta-analyses have assessed the efficacy of NPGS, with inconsistent results [3–5].

To evaluate the efficacy of NPGS techniques, this systematic review was done by conducting a meta-analysis involving relevant published randomized clinical trials of the frequent variations of nonpenetrating surgical procedures in the treatment of open angle glaucoma.

Material and Methods

This meta-analysis was performed according to a predetermined protocol describing complete and detailed methods, which followed 3 previous publications [6–8].

Outcome measures

The primary outcome was the percentage IOP reduction from preoperative to postoperative (IOPR%). When authors reported mean and standard deviation (SD) of IOP and IOPR, we used them directly. When not available, we computed them according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions: [9] $IOPR = IOP_{baseline} - IOP_{endpoint}$ and $SD_{IOPR} = (SD^2_{baseline} + SD^2_{endpoint} - SD_{baseline} \times SD_{endpoint})^{1/2}$. $IOPR\% = IOPR / IOP_{baseline}$ and $SD_{IOPR\%} = SD_{IOPR}/IOP_{baseline}$. For efficacy, the proportion of complete success was also used. Complete success was defined as target endpoint IOP (usually less than 21 mm Hg) without medications.

We also assessed the tolerability of the nonpenetrating procedures by considering the proportion of patients with postoperative complications including hyphema, shallow/flat anterior chamber, hypotony, choroidal detachment, and cataract.

Search strategy

Published randomized clinical trials were identified through a systematic search of PubMed, EMBASE, and the Cochrane Controlled Trials Register. The keywords for the intervention were *canaloplasty*, *deep sclerectomy*, *viscocanalostomy*, *nonpenetrating filtering surgery*, *nonpenetrating trabecular surgery*, *nonpenetrating glaucoma surgery*, *explode Trabecular Meshwork/* all subheadings, and *explode Sclerostomy/*all subheadings. The keywords for the disease were *glaucom*, and explode Glaucoma/* all subheadings. The limit for the search was *clinical trial*. The reference lists of original reports and review articles retrieved through the search were reviewed for additional studies not yet included in the computerized databases.

Trials selection

Published clinical trials were selected based on the protocol-determined selection criteria. (i) Study type: Randomized clinical trials, including placebo- or active-controlled. (ii) Population: All patients with a diagnosis of open angle glaucoma, including primary and secondary. (iii) Intervention: One of all the nonpenetrating surgical procedures was undertaken. Implants or/and antimetabolites could have been used intraoperatively, but, no other surgical procedures were combined. (iv) Outcome variables: at least 1 of the following outcome variables: IOPR%, and complete success rates. (v) Duration: Follow-up time of not less than 6 months postoperatively. (vi) Publication parameters: Written in any language. The original search was performed in December 2009, and regular alerts every 3 months were established. The title and abstract of all potentially relevant articles were screened to determine their relevance, and then full articles were scrutinized if the title and abstract were ambiguous. Two reviewers (JWC, SWC) conducted searches independently.

Data extraction

Data extraction was performed according to the customized protocol by 2 reviewers (JWC, SWC) independently. Any disagreement was resolved by discussion. A customized form for data extraction was used to record the authors of the study, the year of publication, information on study design (whether randomization, allocation concealment, intention to treat analysis, double blind or single blind, parallel or crossover), location of trial, length of study, number of subjects, patient age, sex, and IOP measurements. In addition, we recorded the proportion of withdrawals.

Qualitative assessment

Methodological quality was evaluated (in duplicate by JWC and SWC) using the Delphi list on a scale from 0 to 20 [10]. Items specifically important for interpreting surgical procedures and IOP measurements were also added (Table 1). Each item in this quality list had the same weight. For each publication, a quality score was calculated, where "yes" was scored as 1 point for a certain quality item and "no" and "do not know" were scored as 0 points.

Statistical Analysis

Outcome measure was assessed on an intent-to-treat (ITT) basis, the ITT population comprising all randomized patients who received a minimum of 1 dose of active treatment and provided a valid baseline measurement.

We calculated the IOPR% and complete success rates for the following subgroups: deep sclerectomy (DS), deep sclerectomy with implant (DS-I), deep sclerectomy with mitomycin C (DS-MMC), viscocanalostomy (VCO), viscocanalostomy with implant (VCO-I), and viscocanalostomy with mitomycin C (VCO-MMC). Results of the arms of trabeculectomy (TE) and trabeculectomy with mitomycin C (TE-MMC) were

Table 1. Quality items of the quality assessment system of methodological characte ristics.

Itemcode	Quality item	No. of trials scored "Yes"	References
A	Was a method of randomization performed?	29	12–40
B	Was the treatment allocation concealed?	4	17,19,26,34
C	Was the participants blinded?	2	39,40
D	Was the investigators blinded?	0	
E	Was the examiners blinded?	4	13,19,23,35
F	Were inclusion criteria specified?	28	12–19,21–40
G	Were exclusion criteria specified?	25	12–19,21–33,35,38–40
H	Were all operations performed by the same surgeons?	18	12–20,23–26,33,35,38–40
I	Were the surgical techniques described explicitly?	29	12–40
J	Was postoperative management standardized?	23	12–17,19–28,34–38
K	Were point estimates and measures of variability presented for the primary outcome measures?	29	12–40
L	Was the period of outcome measurements equal for all groups?	28	12–33,35–40
M	Were times of IOP measurements equal for all-groups?	28	12–33,35–40
N	Was IOP measured with Goldmann applanation tonometry?	15	16–18,20,22,24,26,28–31,33,36,37,40
O	Was information about the method of IOP measurement presented?	1	21
P	Were the groups similar at baseline regarding the most important prognostic indicators?	29	12–40
Q	Was it unlikely that compliance may explain differences between groups?	29	12–40
R	Was the withdrawal/drop-out rate described explicitly	9	12,15,17,19,24,26,28,34,35
T	Was the sample size justification described	6	19,33–35,39,40
U	Was an intention-to-treat analysis performed?	1	34

IOP – intraocular pressure.

also calculated as controls. We stratified the analysis of efficacy data by duration of follow-up, including 6, 12, 24, 36, and 48 months. Pooled values were calculated using the DerSimonian and Laird estimate method of the random effects model [11]. The statistical analyses were carried out by Comprehensive Meta-Analysis software version 2.0 (Biostat, Englewood Cliffs, New Jersey) (*http://www.meta-analysis.com*).

We also calculated the qualified success rates, which were defined as target endpoint IOP with or without medications. To evaluate the effect of postoperative interventions, we sub-analyzed the complete success rates of NPGS by the use of goniopuncture.

Results

Study eligibility

The literature search identified 293 articles, and 52 articles were retrieved. Overall, 23 trials were excluded for reasons that included 13 non-randomized trials, 4 surgical combination, 3 inconsistent subjects, 1 duplicate publication, 1 without measure outcomes, 1 irrelevant intervention, and 1 short-term results. Hence, 29 randomized clinical trials were included in the meta-analysis [12–40]. Eight arms were reporting DS; 10 arms were reporting DS-I; 10 arms were reporting DS-MMC; 10 arms were reporting VCO; 1 arm was reporting VCO-I; 12 arms were reporting TE; and 5 arms were reporting TE-MMC.

The characteristics of the eligible studies are summarized in Table 2. Overall, 1455 patients were evaluated. Among the 1287 patients for whom data on age were available, the mean age was 52 years (range, 53-79 years). Among the 1287 patients for whom data on age were available, 703 (54.6%) were male and 584 (45.4%) were female. In general, the quality of included studies was high (Table 2). The mean total quality score for all studies was 58.8% (range, 50–75%).

Intraocular pressure-lowering effects

The random effects pooled estimates of the percentage IOP reductions are shown in Table 3. Pooled results for DS were

Table 2. Baseline characteristics of eligible randomized clinical trials.

Reference	Location	Intervention	End Point measurement (months)	Total No.	Mean age (years)	Sex (M/F)	Baseline IOP (mm Hg) [mean (SD)]	Quality score (%)
El Sayyad et al. 2000 [12]	Saudi Arabia	DS; TE	12	39	53	15/24	28.1 (5.4)	60
Chiselita et al. 2001 [13]	Romania	DS; TE	18	17	60	9/8	27.5 (2.2)	60
Jonescu-Cuypers et al. 2001 [14]	Germany	VCO; TE	6	20	63	11/9	29.7 (6.5)	55
Kozobolis et al. 2002 [15]	Greece	DS; DS-MMC	36	90	68	41/49	26.7 (4.2)	60
Lüke et al. 2002 [16]	Germany	VCO; TE	12	60	61	29/31	27.1 (7.1)	60
O'Brart et al. 2002 [17]	United Kingdom	VCO; TE	19	50	65	32/18	24.1 (6.6)	70
Wang et al. 2002 [18]	China	DS-RHAI; TE	6	168	NR	NR	32.2 (4.7)	55
Carassa et al. 2003 [19]	Italy	VCO; TE	24	50	68	20/30	23.8 (7.0)	75
D'Eliseo et al. 2003 [20]	Italy	DS-RHAI; PDS-RHAI	12	42	75	23/19	23.2 (2.9)	50
Kobayashi et al. 2003 [21]	Japan	VCO; TE-MMC	12	25	63	11/14	24.9 (2.4)	55
Lüke et al. 2003 [22]	Germany	VCO; VCO-RHAI	12	40	61	33/7	26.5 (6.1)	55
Cillino et al. 2004 [23]	Italy	DS; TE	24	35	70	17/18	31.2 (11.7)	60
Egrilmez et al. 2004 [24]	Turkey	DS-TI; VCO; TE	6	34	62	21/13	28.6 (11.1)	65
Neudorfer et al. 2004 [25]	Israel	DS-CI; DS-CI-MMC	24	26	67	13/13	29.0 (4.9)	55
O'Brart et al. 2004 [26]	United Kingdom	VCO; TE	24	50	60	35/15	26.7 (7.3)	70
Ravinet et al. 2004 [27]	Switzerland	DS-TI; DS	24	22	76	7/15	25.8 (12.5)	50
Schwenn et al. 2004 [28]	Germany	DS-RHAI-MMC; TE-MMC	12	22	68	11/11	25.1 (10.1)	60
Shaarawy et al. 2004 [29]	Switzerland	DS-CI; DS	48	104	72	53/51	24.5 (6.4)	50
Yalvac et al. 2004 [30]	Turkey	VCO; TE	36	50	60	36/14	36.9 (8.5)	55
Shaarawy et al. 2005 [31]	Switzerland	DS-CI; DS	54	13	79	3/10	24.7 (4.5)	55
Huang et al. 2006 [32]	China	DS-MMC; TE-MMC	48	105	59	64/41	28.4 (8.4)	50
Mansouri et al. 2006 [33]	Austria	DS-PMMAI; DS-CI	30	53	70	22/31	21.2 (7.4)	60
Mielke et al. 2006 [34]	Nigeria	DS; DS-MMC	24	39	59	29/10	28.1 (7.2)	55
Cillino et al. 2008 [35]	Italy	DS-MMC; TE-MMC	48	40	70	20/20	28.8 (5.9)	70
Leszczyński et al. 2008 [36]	Poland	DS-RHAI-MMC; VDS-RHAI-MMC	12	50	58	36/14	23.8 (3.0)	50
Russo et al. 2008 [37]	Italy	DS-RHAI-MMC; TE-MMC	48	93	67	47/46	25.7 (2.9)	55
Gilmour et al. 2009 [38]	United Kingdom	VCO; TE	60	43	64	29/14	25.2 (4.0)	55
Mansouri et al. 2009 [39]	Switzerland	DS-MMC; DS-D-MMC	24	25	73	10/15	21.1 (8.0)	60
Mansouri et al. 2009 [40]	Switzerland	DS-CI; VDS-CI	24	50	67	26/24	21.4 (6.4)	75

M – male; F – female; IOP – intraocular pressure; SD – standard deviation; DS – deep sclerectomy; VCO – viscocanalostomy; TE – trabeculectomy; CI – collagen implant; RHAI – reticulated hyaluronic acid implant; TI – T-flux® implant; PMMAI – polymethylmethacrylate implant; MMC – mitomycin C; D-MMC – mitomycin C applied under the deep sclera flap; PDS – combined deep sclerectomy and phacoemulsification; VDS – very deep sclerectomy; NR – not reported.

Table 3. The percentage reductions in intraocular pressure from preoperative to postoperative.

Group	6 Months			12 Months			24 Months			36 Months			48 Months		
	No. of arms	Mean (%)	95% CI (%)	No. of arms	Mean (%)	95% CI (%)	No. of arms	Mean (%)	95% CI (%)	No. of arms	Mean (%)	95% CI (%)	No. of arms	Mean (%)	95% CI (%)
DS	7	39.5	33.4 to 45.5	7	37.8	31.9 to 43.8	4	35.2	30.0 to 40.4	2	34.7	20.1 to 49.3	2	39.9	32.6 to 47.2
DS-I	9	42.7	38.9 to 46.5	8	40.1	34.9 to 45.3	4	41.1	29.2 to 52.9	1	52.0	47.3 to 56.7	1	50.4	45.9 to 54.9
DS-MMC	7	43.7	41.4 to 46.1	8	42.6	37.8 to 47.5	6	41.7	37.8 to 45.6	4	39.8	36.8 to 42.9	3	36.2	30.2 to 42.2
VCO	10	37.1	32.4 to 41.7	8	32.1	27.2 to 37.1	4	30.2	23.1 to 37.3	2	38.9	16.2 to 61.7	1	32.7	26.2 to 39.2
VCO-I	1	39.3	30.5 to 48.1	1	35.1	26.5 to 43.7	0	NA	NA	0	NA	NA	0	NA	NA
TE	10	46.0	42.0 to 50.0	7	45.8	40.1 to 51.4	4	45.6	40.0 to 51.1	2	51.0	38.7 to 63.2	1	50.6	44.5 to 56.7
TE-MMC	5	47.6	43.2 to 52.1	5	45.3	42.1 to 48.5	3	42.7	40.1 to 45.3	3	42.2	39.6 to 44.7	3	41.0	36.5 to 45.4

DS – deep sclerectomy; VCO – viscocanalostomy; TE – trabeculectomy; I – implant; MMC – mitomycin C; CI – confidence interval; NA – not applicable.

Table 4. The proportion of patients with target endpoint intraocular pressure without medication.

Group	6 Months			12 Months			24 Months			36 Months			48 Months		
	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)
DS	4	71.8	49.6 to 86.9	5	66.1	47.9 to 80.5	4	44.0	18.9 to 72.5	1	37.8	24.9 to 52.6	2	35.4	24.8 to 47.7
DS-I	5	93.5	79.6 to 98.1	6	66.2	53.1 to 77.3	5	59.5	34.0 to 80.8	1	24.9	15.0 to 38.4	2	64.6	52.3 to 75.2
DS-MMC	4	88.9	82.0 to 93.3	7	70.6	56.6 to 81.5	5	41.3	22.9 to 62.5	3	60.5	43.2 to 75.5	3	52.1	43.1 to 61.0
VCO	8	61.5	43.9 to 76.5	8	52.6	41.3 to 63.6	4	43.9	24.6 to 65.2	2	32.1	20.3 to 46.7	1	22.7	9.8 to 44.4
VCO-I	1	45.0	25.3 to 66.4	1	40.0	21.4 to 62.0	0	NA	NA	0	NA	NA	0	NA	NA
TE	6	79.8	60.4 to 91.1	6	73.2	56.9 to 84.9	4	62.1	49.4 to 73.4	2	52.2	37.9 to 66.1	1	47.6	27.9 to 68.2
TE-MMC	2	90.0	81.3 to 94.9	3	82.5	71.7 to 89.8	1	80.4	67.9 to 88.8	2	74.5	65.4 to 81.9	3	70.0	61.5 to 77.4

DS – deep sclerectomy; VCO – viscocanalostomy; TE – trabeculectomy; I – implant; MMC – mitomycin C; CI – confidence interval; NA – not applicable.

39.5% at 6 months, 37.8% at 12 months, 35.2% at 24 months, 34.7% at 36 months, and 39.9% at 48 months. Pooled estimates for VCO were 37.1% at 6 months, 32.1% at 12 months, 30.2% at 24 months, 38.9% at 36 months, and 32.7% at 48 months. Both DS and VCO were less effective in lowering IOP than was TE. Intraoperative adjunctive use of implants and mitomycin C increased IOP-lowering effects of DS and VCO.

Complete success rate

The random effects pooled estimates of the complete success rates are shown in Table 4. Pooled results for DS were 71.8% at 6 months, 66.1% at 12 months, 44.0% at 24 months, 37.8% at 36 months, and 35.4% at 48 months. Pooled estimates for VCO were 61.5% at 6 months, 52.6% at 12 months, 43.9% at 24 months, 32.1% at 36 months, and 22.7% at 48 months. Both DS and VCO were associated with smaller complete success rates compared with TE. Intraoperative use of implants and mitomycin C also increased the proportions of patients who achieved target IOP without medications of DS and VCO.

Postoperative intervention

The postoperative use of glaucoma medicines significantly increased the success rates of all procedures. The qualified success rates at end point were 71.7% for DS, 94.0% for DS-I, 78.0% for DS-MMC, 73.7% for VCO, 85.0% for VCO-I, 90.8% for TE, 87.5% for TE-MMC, all of which were greater than the complete success rates (Table 5).

Fourteen trials reported that goniopuncture were used postoperatively [12,17,19,21,26,27,29,31,33,35,36,38–40]. The pooled subgroup estimates of the complete success rates are shown in Table 6. For DS, DS-MMC, and VCO, the pooled results of goniopuncture-used trials were greater than those of trials without goniopuncture intervention.

Postoperative complication

The rates of main postoperative complications, including hyphema, shallow/flat anterior chamber, hypotony, choroidal detachment, and cataract, were lower in NPGS-treated eyes than those in TE-treated eyes (Table 7).

Table 5. The complete and qualified success rates at end point.

Group	Complete Success Rate			Qualified Success Rate		
	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)
DS	9	43.9	27.8 to 61.5	9	71.7	64.6 to 77.8
DS-I	9	61.7	44.7 to 76.3	9	94.0	86.1 to 97.5
DS-MMC	8	48.5	34.3 to 63.0	6	78.0	55.0 to 91.1
VCO	9	40.3	27.0 to 55.3	9	73.7	66.1 to 80.1
VCO-I	1	40.0	21.4 to 62.0	1	85.0	62.4 to 95.1
TE	11	70.3	58.0 to 80.2	11	90.8	85.4 to 94.4
TE-MMC	4	71.8	62.9 to 79.3	3	87.5	78.8 to 93.0

DS – deep sclerectomy; VCO – viscocanalostomy; TE – trabeculectomy; I – implant; MMC – mitomycin C; CI – confidence interval.

Table 6. The complete success rates at end point of subgroups by the use of goniopuncture.

Group	Goniopuncture Intervention			No Goniopuncture Intervention		
	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)
DS	4	61.6	30.7 to 85.3	5	32.1	17.0 to 52.1
DS-I	5	57.6	41.8 to 72.0	4	68.3	27.0 to 92.7
DS-MMC	3	73.3	46.5 to 89.6	5	38.2	27.0 to 50.8
VCO	5	47.4	26.3 to 69.4	4	33.2	23.2 to 45.0

DS – deep sclerectomy; VCO – viscocanalostomy; I – implant; MMC – mitomycin C; CI – confidence interval.

Table 7. The proportion of patients with postoperative complications.

Group	Hyphema			Shallow/flat anterior chamber			Hypotony			Choroidal detachment			Progressive cataract		
	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)	No. of arms	Rate (%)	95% CI (%)
DS	8	12.4	7.8 to 19.2	6	2.9	1.0 to 7.9	5	4.3	0.7 to 22.1	5	10.2	6.0 to 16.7	5	12.7	4.6 to 30.9
DS-I	8	5.5	2.9 to 10.0	4	3.8	1.1 to 12.3	6	3.5	1.4 to 8.5	7	7.3	4.0 to 13.1	7	14.9	8.3 to 25.5
DS-MMC	6	13.7	8.8 to 20.7	4	11.0	4.0 to 26.9	4	8.2	0.5 to 60.1	5	11.6	4.8 to 25.5	1	4.7	1.2 to 16.8
VCO	8	11.1	6.2 to 19.2	6	7.0	3.5 to 13.5	8	6.6	2.4 to 16.9	4	2.0	0.5 to 7.6	7	9.2	1.5 to 41.1
VCO-I	1	10.0	2.5 to 32.4	1	10.0	2.5 to 32.4	1	25.0	10.8 to 47.8	1	5.0	0.7 to 28.2	1	2.4	0.1 to 28.7
TE	10	16.8	9.1 to 29.0	7	20.7	13.0 to 31.3	9	17.1	9.5 to 28.9	4	16.7	10.3 to 25.9	6	15.3	8.5 to 25.9
TE-MMC	4	16.3	5.5 to 39.6	5	22.4	8.8 to 46.2	5	20.4	7.8 to 43.5	3	19.3	7.7 to 40.7	2	14.7	7.2 to 27.7

DS – deep sclerectomy; VCO – viscocanalostomy; TE – trabeculectomy; I – implant; MMC – mitomycin C; CI – confidence interval; NA – not applicable.

Discussion

In the present meta-analysis, we reviewed 29 randomized clinical trials and confirmed that deep sclerectomy and viscocanalostomy lower IOP in patients with open angle glaucoma, and also were capable of achieving target IOP without medications. However, both nonpenetrating glaucoma surgeries were less effective than trabeculectomy in lowering IOP. Intraoperative use of implants and mitomycin C increased the IOP-lowering effects of deep sclerectomy.

Several previous meta-analyses have assessed the efficacy of NPGS [2–5,41]. We published the first meta-analysis on the same subject, in which totally 37 article were reviewed,

including randomized clinical trials, prospective series of cases, and retrospective studies, and only the pooled complete success rates were estimated [4]. The other 3 meta-analyses, which we published previously, examined the trials with direct comparisons between NPGS and TE, with or without intraoperative implants and mitomycin C application [2,4,41]. The recent meta-analysis, which reviewed the reports in the last 5 years, simply calculated the complete success rates, but did not use the statistics of a usual meta-analysis. Also, the previous meta-analyses did not separate the studies by their level of scientific evidence and by the length of follow-up, which can influence the study results [42]. The present meta-analysis, which reviewed 29 articles, included only the randomized clinical trials with separation according to the duration of follow-up, and calculated the mean for a series of parameters – relative reduction in IOP and relative frequency of cases reaching target IOP – using a rigorous statistical method.

Both deep sclerectomy and viscocanalostomy significantly lowered IOP in open angle glaucoma, with mean relative IOP reductions of more than 30%. The percentages of cases achieving target IOP after primary DS were 66.1% at 1 year, 44.0% at 2 years, 37.8% at 3 years, and 35.4% at 4 years. The complete success rates after primary VCO were 52.6% at 1 year, 44.9% at 2 years, 32.1% at 3 years, and 22.7% at 4 years, which was quite close to that after primary DS up to 3 years. However, higher complete success rates were achieved after primary trabeculectomy – 73.2% at 1 year, 62.1% at 2 years, 52.2% at 3 years, and 47.6% at 4 years. Therefore, the degree and longevity of IOP-lowering after both NPGS were still lower than those after trabeculectomy.

Use of an implant during NPGS is thought to enhance success by helping to maintain a low-pressure intrascleral lake between the external flap and trabecular meshwork, acting as a space maintainer during the time of maximal healing. Several commercially available implants (Aqua-flow collagen drainage device, T-flux, SKGEL and PMMA implant) have been developed, and these appear to be equally efficacious [43]. The present meta-analysis suggests that IOP control might be better when implants are used intraoperatively. The percentage IOP reduction after DS with implants was 50.4% at 4 years, and the complete success rate after DS with implants was 64.6% at 4 years, both of which were higher than those after primary DS and more similar to that of trabeculectomy.

Mitomycin C is an antiproliferative drug used during the initial stages of glaucoma surgery to prevent the conjunctiva healing onto the sclera. A previous systematic review suggested that the intraoperative MMC application can reduce the failure risk of conventional trabeculectomy [44]. In the present meta-analysis, the IOP-lowering effect of DS with MMC was greater than that of primary DS, with 52.1% of cases achieving target IOP at 4 years. Because NPGS is an external filtering procedure, it follows that the use of antiproliferatives is associated with higher surgical success.

The results of the present meta-analysis indicated a gradual loss of IOP-lowering effect after NPDS, over time. More postoperative interventions, such as antiglaucoma medications and goniopuncture, were necessary to maintain the IOP-lowering effect of NPGS. In the present meta-analysis, we also evaluated the effect of additional interventions and found that the postoperative use of either antiglaucoma medication or goniopuncture increased the success rate of NPGS. Therefore, there was a possibility for bias in the efficacy of NPGS because of the use of additional interventions in many included trials.

The main reason for developing new filtration surgery techniques as an alternative to trabeculectomy is to overcome possible complications. The previous meta-analysis found that the nonpenetrating surgical procedures offered such an advantage when compared with trabeculectomy [2]. In the present meta-analysis, we also found that NPGS and its modifications were less likely to cause major postoperative complications than was trabeculectomy. The incidence of cataract was also lower in NPGS-treated eyes than that in TE-treated eyes. The other severe complications, such as persistent corneal edema and persistent bleb leaks, were rare in the NPGS group. Therefore, nonpenetrating surgical procedures were better tolerated than was TE.

Disadvantages of meta-analyses include acknowledged and covert duplication of data, and publication bias. In order to avoid acknowledged and covert duplication of data, 2 independent researchers judged the eligibility of articles and extracted data from the eligible articles. In an attempt to reduce publication bias, we searched in multiple databases and websites, and publications in any language were included. In addition, the differences in lengths of follow-up may contribute to the variety of results. To avoid potential source of heterogeneity based on data pooled from trials of different durations, we separated the studies into subgroups' by the length of follow-up.

The present study has limitations that stem from the designs of the individual trials, as well as the methods of the meta-analysis itself. First, most of trials lacked adequate allocation concealment, blinding, and sample size assessment, which may leave them vulnerable to bias and overestimation of the beneficial effects of IOP-lowering interventions. However, given the homogeneity of results across studies, it is unlikely that a few poorer-quality trials significantly biased the pooled estimates. Second, several pooled data sets are based on only a few papers, especially those beyond 3 years, and more research is needed on the available guidance derived from the current literature. Third, there is great variation in the success criteria and target IOPs. The Advanced Glaucoma Intervention Study (AGIS) and the Collaborative Initial Glaucoma Treatment Study (CIGTS) are the prospective randomized 'gold-standard' clinical trials, which have provided data and evidence that achievement of properly set target IOPs according to glaucoma severity is required to stop disease progression [45,46]. A target IOP of 21mm Hg is widely used as an outcome measure in clinical trials, which is misleading [3]. Therefore, further research is still needed to fully determine the validity, reliability, and sensitivity in choosing the best one. Finally, many studies were of modest size, and generalization is therefore limited.

Conclusions

This meta-analysis suggests that deep sclerectomy and viscocanalostomy can provide IOP reduction in open angle glaucoma, with relative IOP reductions of more than 30% and complete

success rate of over 20% at 4 years. However, the degree and longevity of IOP-lowering after primary NPGS are still lower than those after primary trabeculectomy. Intraoperative use of implants and mitomycin C in NPGS appear to result in improved intraocular pressure control, when compared with NPGS alone, and helped the results approach the success rate for trabeculectomy. In the future, longer-term clinical trials with target IOPs that reflect clinical practice are needed to evaluate the efficacy of NPGS and its modifications.

Conflict of Interest

None.

Financial Disclosures

None.

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