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ORIGINAL ARTICLE

Comparing the safety and efficacy of intracameral tissue plasminogen activator (t-PA) in trabeculectomy with MMC Vs standard trabeculectomy with MMC only.

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ABSTRACT… Objective: To find out the harmlessness and effectiveness of intra-cameral tissue plasminogen activator (t-PA) in trabeculectomy for patients with primary open angle glaucoma (POAG). **Study Design:** Quasi-experimental Trial. **Setting:** Eye B Department, of Khyber Teaching Hospital, Peshawar. **Period:** Jan. 2021 and Dec. 2021. **Material & Methods:** Patients with POAG, who were operated for trabeculectomy (trab.) Two groups were created out of study population i.e. Trab-MMC (Trab. With MMC done) and Trab-MMC/t-PA (Trab. With MMC + intra-cameral t-PA done). Success was defined as eyes having pressure (IOP) within the range of 8-20mmHg with at-least 25% reduction from pre-op IOP achieved with or without IOP lowering drugs. **Results:** Out of 20 participants (08 women and 12 men) 10 were allocated to each gp. Pre-op IOP was 28 ± 4.6 mmHg and 27 ± 4.8 mmHg, which dropped to 12.6 ± 3.8 mmHg and 11.1 ± 1.6 mmHg at 1st yr. post-op ($p < 0.05$) for both gps respectively. Surgical success was attained in 66% of Trab-MMC as compared to 86 % Trab-MMC/t-PA at 1st yr. ($p = 0.44$). Success with medication was 86 % compared to 100 % at 1st yr. respectively ($p = 0.28$). We didn't observe any adverse effects with the use of intra-cameral t-PA. **Conclusion:** Adjunctive use of intra-cameral t-PA in trabeculectomy with MMC can result in improved outcome as compared to procedure without it. No side effects were noted with intra-cameral use of t-PA.

Key words: Mitomycin-C, Primary Open Angle Glaucoma, Tissue Plasminogen Activator, Trabeculectomy.

INTRODUCTION

Cairn performed 1st trabeculectomy (trab.) in late 60s and from than onwards this procedure is considered to be the gold standard for advanced glaucomatous eyes with progressive field loss refractory to medications or laser-trabeculoplasty by creating a fistulous tract between the anterior chamber and sub-conjunctival space for free flow of the aqueous.[1,2,3] The main cause of the procedure failure is the formation of scar tissue by the fibroblasts at the sclerectomy site impeding the flow of aqueous in the sub-conjuctival space[4,5] Formation of granulation tissue by the activated fibroblasts as a part of healing response plays a vital role in filtration failure.[6] The fibrinogen is converted into fibrin, the fibrin/fibronectin complex plays a crucial role in scar formation, if this complex can be lysed in the early post-op period than further steps in healing response can be changed thus enhancing the post-op success of trab. Further enthusiasm into the quest for enhanced success of trab. By altering the healing response has resulted in the adjunctive use of anti-metabolites i.e. mitomycin-C (MMC) and 5-fluorouracil (5-FU) which can prevent the proliferation and migration of fibroblasts thus increasing the success of filtration surgeries for glaucomatous eyes.[7.8]

Recombinant tissue plasminogen activator (t-PA) is a serum-protease that catalyzes inactive plasminogen into plasmin, the main degrading enzyme for blood clots via the proteolysis of fibrin into fibrinogen[9,10] In the early 80s t-PA was utilized for various ocular procedures including resolution of sub-retinal hemorrhages and prevention of AC-

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fibrin formation after pediatric cataract surgeries[11] It has also been used in vivo to be very effective in prevention of scarring in various experimental models under controlled environment[9,10,12,14] and few clinical trials have shown its efficacy in treating cystic-blebs post-op.[15-21]

The rationale of this research work is to assess the harmlessness and effectiveness of intra-cameral t-PA in naïve trab. in primary open-angle glaucoma (POAG).

MATERIAL & METHODS

In this quasi-experimental study, we recruited participants with POAG (gonioscopy based) who underwent trabeculectomy at an Eye B dept. of Khyber teaching Hospital, Peshawar between Jan. 2021till December 2021. The study was according to the tenets of declaration of Helsinki and good clinical practice. An ethical approval was granted to us by the institutional ethical review board (IERB) with approval no. 3486/IERB/R&D/KMC. An informed consent was acquired from all the participants of trial.

Our study population included participants who were ≥18 yrs. of age. All those with a previous history of globe injury or any ocular procedures performed in the past were not selected for trial. Participants were allocated into two groups: group i.e. Trab-MMC (Trab. With MMC done) and Trab-MMC/t-PA (Trab. With MMC + intra-cameral t-PA done). A simple randomization by lottery method was used for grouping.

Steps of the Procedure

All surgeries were performed by single surgeon. The steps included conjunctival and tenon exploration at 12 o'clock with toothed conjunctival scissor approx. 6mm away from the limbus and leaky blood vessels were cauterized with bipolar cautery-lead. A rectangular 2/3rd scleral-flap thickness was dissected by using a crescent knife. A cellulose-sponge dipped in MMC with concentration of 0.02 mg/0.1cc and placed flap for 3-min and afterwards washed with ringer lactate solution. A limbal side port was created by using a 15º knife, and viscoelastic gel i.e. Hydroxypropyl methyl cellulose (HPMC) was injected into the anterior chamber. A peripheral iridectomy (PI) was made at 12 o'clock with vannus sissor after making a small sclerectomy under scleral flap. The scleral-flap was stitched with silk 8/0 sutures at its free ends, in the same way conjunctiva was closed with silk 8/0 sutures. In Trab-MMC/t-PA gp. 30μg/0.1cc t-PA was injected with a 26G visco-cannula intracamerally via side port.

Post-op Schedule

Post-op, participants were prescribed Moxifloxacin 0.5% eye drops plus dexamethasone sodium phosphate 0.1% combination eye drops 4 times daily for 2 weeks, which were tapered down slowly over the subsequent 4 to 6 weeks. Post-op visits were done at 1st day, 1st, 4th and 12th week followed by assessment at 6th month and final examination was done at 1st year post-op. The best corrected visual acuity (BCVA), IOP measurement and slit-lamp examination and assessment of the bleb including checking for any leakage by doing siedel, s test were conducted during the follow ups. Humphrey visual-field analysis (24-2) was conducted twice during the one yr. follow up period.

Study variables

The prime outcome variable taken was surgical/procedural IOP reduction (in terms of success) at 6th & 12th month post-op, defined as an IOP reduction of at-least 25% from pre-op IOP to a measured pressure within range of 08-20mmHg with at-least light-perception visual acuity, without pressure lowering drugs.

The 2ndry outcome was success with medication, defined as attainment of low IOP with pressure lowering drugs. The procedure was considered failure, when the target IOP wasn't achieved with pressure lowering drugs/ worsening to light perception only vision and or the need for redo trab. /needling or implanting glaucoma drainage devices/valves for IOP reduction.

Statistical Analysis

All the statistical analysis were done by using SPSS version 26.0 (IBM corp. USA). Continuous and quantitative variables like age, BCVA, IOP and no. of IOP lowering drugs were expressed

as means ± SD, while categorical/ qualitative variables like gender and glaucoma type were expressed as frequencies and percentages for statistical analysis.

Within the group analysis was done by using paired-samples T-test, while between the groups analysis was conducted by running Mann–Whitney test. Statistical significance was taken at $p < 0.05$.

RESULTS

Twenty (20) participants (8 women &12 men) were selected for the trial. Ten (10) subjects were randomly allocated into each group. Average age of Trab-MMC was 60.44 ± 11.76 yrs. compared to 61.24 ± 10.6 yrs. in Trab-MMC/t-PA. Pre-op demographics are shown in Tabel-I.

	Trab-MMC group (n=10)	Trab-MMC/t-PA group (n=10)
Age in yrs. ± SD	60.44±11.76	61.24±10.6
Gender		
Men (%)	04 (40.0%)	05 (50.0%)
Women (%)	06 (60.0%)	05 (50.0%)
Glaucoma type		
POAG	07 (70.0%)	09 (90.0%)
PXF	03 (30.0%)	01 (10.0%)
Pre-op Values		
IOP±SD (mmHg)	28.0 ± 4.6	27.0 ± 4.8
No. of anti-glaucoma e/d ±SD	3.0 ± 0.8	3.2 ± 1.1
BC-VA (Log-MAR) ±SD	0.4 ± 0.2	0.4 ± 0.5

Table-I. Patients demographics and pre-op findings

POAG primary open-angle glaucoma, PXFG pseudoexfoliation glaucoma, IOP intra-ocular pressure, t-PA tissue plasminogen activator, BC-VA best-corrected visual acuity

IOP Changes

IOP was 28 ± 4.6 mmHg and 27 ± 4.8 mmHg at baseline; 14.2 ± 3.9 mmHg and 10.1 ± 2.4 mmHg ($p = 0.06$) at 6th month and 12.6 ± 3.8 mmHg and 11.1 ± 1.6mmHg ($p= 0.08$) at 12th month for Trab-MMC & Trab-MMC/t-PA respectively. IOP reduction was statistically significant ($p <0.05$) in both groups at 6th &12th month compared to pre-op values. The IOP values of the treatment arms are displayed in Table-II.

	Trab-MMC (n=10)	Trab-MMC/t-PA (n=10)	P-Value
Pre-op value	28.0 ± 4.6	27.0 ± 4.8	0.84
1st week	10.2 ± 2.7	10.9 ± 3.9	0.72
1st month	14.1 ± 7.6	13.4 ± 6.6	0.08
3rd month	15.2 ± 7.8	12.5 ± 3.2	0.07
6th month	14.2 ± 3.9	10.1 ± 2.4	0.06
12th month	12.6 ± 3.8	11.1 ± 1.6	0.08

Table-II. Intra-ocular pressure (mmHg) at different follow ups.

t-PA tissue plasminogen activator

Procedure Outcomes

Procedural success at 6th month was 80 % in Trab-MMC and 95 % in Trab-MMC/t-PA ($p = 0.11$). At 12th month 66% of Trab-MMC attained surgical success vs. 86 % of Trab-MMC/t-PA without medications ($p = 0.44$). Success with medications was achieved in 86 % of Trab-MMC vs. 100 % of Trab-MMC/t-PA at 12th month ($p = 0.28$) as shown in Table-III.

	Trab-MMC (n=10)	Trab-MMC/t-PA (n=10)	P-Value
Surgical success (%) at 6th month	80.0	95.0	0.11
Surgical success (%) at 12th month	66.0	86.0	0.44
Success with medications (%) at 12th month	86.0	100.0	0.28

Table-III. Success rate of two groups.

At 12th month two patients in Trab-MMC and no patient in Trab-MMC/t-PA had failed filtration. In those two (2) cases target-IOP was not achieved despite medications. The number of pre-op IOP lowering drugs for Trab-MMC was 3.0 ± 0.8 compared to 3.2 ± 1.1 for Trab-MMC/t-PA ($p = 0.51$). At final visit, the no. of eye drops fell to 1.0 ± 0.8 compared to 0.6 ± 0.8 respectively ($p = 0.62$). All cases of raised IOP occurred after 12th week post-op.

Argon-suture lysis was done in 3 (30%) patients in Trab-MMC and in one (10%) patient in Trab-MMC/t-PA ($p = 0.32$). Adjunctive t-PA didn't affect adverse effects like hyphema / hypotony or the need for secondary procedure.

DISCUSSION

In this prospective clinical trial, we selected subjects having POAG and categorized them into two groups' i.e. Trab-MMC and Trab-MMC/t-PA to evaluate the efficacy of intra-cameral t-PA in procedure outcome (success). We observed IOP at 6th month was 14.1 ± 3.9 mmHg and 10.1 ± 2.8mmHg and at 12th month 12.6 ± 3.8 mmHg and 11.1 ± 1.6mmHg for Trab-MMC and Trab-MMC/t-PA respectively. At 12th month of follow-up, surgical success was achieved in 66% of subjects in Trab-MMC and 86% of Trab-MMC/t-PA gp. and success with medication was 86% in the Trab-MMC vs. 100% in Trab-MMC/t-PA group. Due to small sample size of our study we couldn't achieve any statistically significant difference between the groups, however there was slightly reduced IOP with better filtration in the Trab-MMC/t-PA group. The over-all success rate for Trab-MMC gp. was identical to some past studies done, demonstrating a success rate in the range of 65 to 85%.[2,4,22,23] However, the over-all success rates for Trab-MMC/t-PA gp. was higher, reaching 100%. In trab. Surgery, the goal is to inhibit the fibrosis/healing response to enhance the successful outcome of the procedure in contrast to other surgical procedures where healing is desirable. Earliest step in the wound healing is the lying down of fibrin/fibrinogen clot[12,15], this complex has been isolated from the fistulas of trabeculectomy specimens[16], t-PA is proteases playing a pivotal role in the fibrino-lytic cascade. It can be extracted by natural means as well as by genetic engineering methods via conversion of plasminogen into plasmin which allows brisk fibrinolysis.[9,10]

In the past some trails were conducted by using the t-PA in cases of treating failed blebs in trabeculectomies, however no one used it intra-camerally at the end of procedure as an adjunctive agent.[16,17,20,21,25] As we know of today, some in vitro trails were performed for prevention of granulation tissue by injecting t-PA as an adjunct to trabeculectomy.[9,10,12-14] Fourman and Vaid [12] noted that t-PA by interfering with formation of fibrin, which is important for clot formation, intervenes in natural healing response thus making the filtration bleb of trabeculectomy more effective and long lasting. Fourman and Wiley[14] demonstrated the efficacy of t-PA in rabbit eyes after performing trabeculectomy procedures on them. Deposition of fibro-nectin and collagen-III in the sub-conjunctival tissue of the bleb and along the inner aspect of the fistula tract was delayed, and this delay was associated with persistence of a clinically evident filtering bleb. Jing et al[13] explored the synergistic effect of intra-cameral t-PA along with intra-bleb 5-FU in preventing the healing mechanism in white rabbits. They observed amazing effect of this combination in inhibiting fibrosis in the filtration bleb of trab.

We observed similar incidence of complication in both the study groups. There was neither an evidence of adverse/toxic reaction locally inside an eye nor systemically from the intra-cameral use of t-PA. To our limited knowledge this is the 1st study of its kind done locally, where the efficacy of t-PA in primary Trab-MMC was delineated. Although we found excellent success rates in the t-PA group, but due to the small number of participants we didn't achieve statistically significant results.

Further similar studies are suggested with larger sample sizes and preferably multicenter so as to clearly delineate the efficacy of t-PA as an adjunct agent in Trab-MMC for better IOP control and filtration success.

CONCLUSION

Adjunctive use of t-PA intra-camerally at the end of trabeculectomy may result in improved outcome in terms of better IOP control and filtration success in patients with POAG as compared to trabeculectomy with MMC without it. No, adverse effects were observed with inta-cameral use.

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3	Javed Rasul	Data collection, analysis, interpretation and intellectual content addition.	
4	Muhammad Farhan	Data collection, analysis, interpretation and intellectual content addition.	
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