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CYCLONAMINE IN CATARACT SURGERY*†

A CLINICAL TRIAL

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CYCLONAMINE (diethylammonium 1,4-dihydroxy-3-benzenesulphonate; Dicynone)‡ is a synthetic haemostatic the action of which results from an increase in vascular resistance associated with reduced bleeding time. Raby and Coupier (1965), in a series of cases with increased capillary fragility, showed a favourable increase in vascular resistance after the intravenous injection of 250 mg. cyclonamine. Canal (1964), in a double-blind trial, demonstrated a mean reduction in bleeding time of 33·8 per cent. (placebo 8·1 per cent.) with oral cyclonamine, and in a second group of patients a mean reduction of 32·9 per cent. (placebo 4·5 per cent.) one hour after the intramuscular injection of 500 mg. cyclonamine. Borel (1962) was impressed with the drug in general surgical use, and Volet, Bonhôte, Skouvaklis, and Locher (1963) demonstrated a reduction in blood loss in gynaecological surgery.

In the field of ophthalmology Stucchi and Nouri (1962) treated a controlled series of twenty patients undergoing a variety of operations with intramuscular cyclonamine 500 mg. on the pre-operative day, and 500 mg. 2 hours before operation. They reported a marked reduction of bleeding in 65 per cent. of cases. Vicari (1963) reported a low haemorrhage rate of 6·73 per cent. in 104 cases of cataract, drainage, and sclerectomy (retinal detachment) procedures. These patients received 500 mg. cyclonamine intramuscularly 1 hour pre-operatively, and 250 mg. daily by the same route for two post-operative days. A year later Vicari (1964) published a further series, this time using oral cyclonamine, and was again favourably impressed.

The present trial was carried out to estimate the efficacy of cyclonamine from the practical standpoint of observable reduction in haemorrhage at operation, in comparison with a control group.

Material and Procedure

Selection of Cases.—To facilitate estimation and comparison of bleeding, cataract operations only were included. All extractions from routine operating lists were entered into the trial, the following only being excluded: diabetics, known hypertensives, lens-induced glaucomas, one patient with a highly vascularized cornea, and cases in which the retrobulbar injection leaked subconjunctivally.

A random method based on the hospital card number was used to divide patients into two groups; one group received cyclonamine and the second acted as control.

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‡ British approved name: Ethamsylate (Dicynone).

The cyclonamine group consisted of 91 patients (100 eyes); there were 46 males and 45 females and their ages ranged from 24 to 90 years (average 65). The control group contained 100 patients (118 eyes); 47 males, 53 females, ages from 25 to 85 years (average 63). These ages are necessarily approximate as many patients had no accurate knowledge of their date of birth.

A bilateral cataract extraction was sometimes undertaken in a single theatre session, but for the purpose of this paper each eye is regarded as a separate case.

The hospital organization did not allow for a fully blind trial, but in a large number of cases the surgeon was uncertain at operation from which group his patient came.

Method.—Pre-operatively local sulpha or antibiotic drops were instilled four times daily. In all cases on the morning of operation 120 mg. (2 gr.) phenobarbitone were given orally, those in the cyclonamine group receiving at the same time 250 mg. cyclonamine intramuscularly. The drug is supplied in a 2 ml. ampoule containing 250 mg.

The operation was performed and completed between 1 and 4 hours after pre-medication.

At operation amethocaine eye drops were instilled for 5 minutes, and a 2 ml. retrobulbar injection with facial injections of lignocaine 2 per cent. with 1 in 80,000 adrenaline were given. Adrenaline eye drops were deliberately withheld lest there should be any irregularity in application or response.

Unfortunately, before completion of the trial, supplies of lignocaine with adrenaline ceased completely, and procaine 2 per cent. with 1 in 50,000 adrenaline was substituted. At this point 32 cases (32 per cent.) in the cyclonamine group were still to be treated, and accordingly the control group was continued to a total of 118, at which point 38 cases (32·2 per cent.) had also received the procaine and adrenaline anaesthetic.

Operative Technique.—After the insertion of lid sutures and superior rectus immobilization, a limbus-based conjunctival flap was made, the limbus was incised with a Bard-Parker knife, and the incision extended to 180° with Castroviejo's scissors. In a few cases (15 (15·0 per cent.) in the cyclonamine group, and 15 (12·7 per cent.) in the control group) a 180° von Graefe section with conjunctival flap was performed.

This was followed by peripheral or broad iridectomy and the insertion of three Barraquer silk sutures. The lens was delivered by hand erisophake or forceps, in most cases intracapsularly. After the extraction the sutures were tied, the iris adjusted with a repositor, the conjunctival flap replaced, and in the majority of cases tied with two 3–0 black silk sutures. Air was then introduced into the anterior chamber, and penicillin drops, together with pilocarpine or atropine, were instilled.

All operations were performed by the same surgeon (T.H.), who estimated the blood loss in each case by observation, recording the degree of haemorrhage in grades from 1 + (very minimal bleeding) to 5 + (heavy persistent bleeding). Blood from lid sutures or canthotomy, when performed, was kept from the operative field and disregarded.

No cautery or other local means of haemostasis was employed, except in one case in the control group in which the haemorrhage had already reached 5 + classification.

First dressing was undertaken 24 hours after operation and the presence of hyphaema was recorded. Patients continued to be observed for five post-operative days.

Results

These are depicted graphically in the Figure (opposite), which shows the distribution of bleeding. Although the main object of the trial was to evaluate operative haemorrhage, an account was kept of any post-operative fresh hyphaema. This was taken to be a hyphaema occupying one half or more of the anterior chamber at first dressing, or any fresh bleeding noted during the five post-operative days in hospital. The criterion of a half hyphaema was chosen to avoid interpreting the remnants of operative blood as post-operative bleeding. These findings are shown in comparison with operative haemorrhage in Table I (opposite).

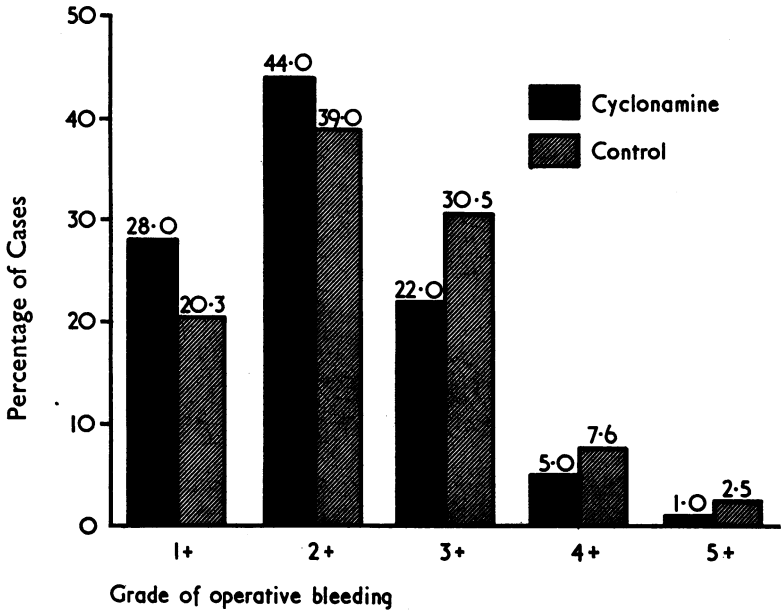

FIGURE.—Grade of operative bleeding in cases and controls.

TABLE I

OPERATIVE BLEEDING IN CYCLONAMINE AND CONTROL GROUPS AND OCCURRENCE OF POST-OPERATIVE HYPHAEMA

Grade of Bleeding	Cyclonamine		Control	
	All Cases	Hyphaema Cases	All Cases	Hyphaema Cases
1+	28	2	24	1
2+	44	2	46	4
3+	22	1	36	2
4+	5	–	9	1
5+	1	–	3	1
Total	100	5 (5·0 per cent.)	118	9 (7·6 per cent.)

The maximum source of operative bleeding was observed to be the corneo-scleral section, and this accounted for almost the entire blood loss. Bleeding from the conjunctival flap in most cases was minimal, but in some eyes persistent. Haemorrhage from the iridectomy was difficult to assess on account of blood from the section covering the iris and the conjunctival flap which lay on the cornea. However, it was slight in comparison with that from other sources. Table II (overleaf) shows the distribution of types of iridectomy. In one patient in the cyclonamine group an iridectomy was present from a previous operation and this was left untouched.

Side-effects

No side-effects were noted, and cyclonamine was extremely well tolerated throughout.

TABLE II
COMPARISON OF IRIDECTOMY IN CYCLONAMINE AND CONTROL GROUPS

Iridectomy	Cyclonamine		Control	
	No.	Per cent.	No.	Per cent.
Peripheral	55	55·0	61	51·7
Broad	44	44·0	57	48·3
Nil	1	1·0	—	—
Total	100	100·0	118	100·0

Analysis and Comment

The statistical analysis is given in greater detail in the Appendix, but the main points will be mentioned here.

The following variable factors were considered to have a possible effect on bleeding: age, sex, retrobulbar injection, corneo-scleral section, iridectomy, and cyclonamine. Analysis was carried out in terms of these factors, and it was revealed that the response to cyclonamine differed in cases in which the von Graefe knife was used from that in the remainder.

Analysis was then repeated under the headings of "Graefe cases" and "knife and scissors" cases, and five groups of eyes emerged (Table III):

(1) Graefe section
(2) Knife and scissors section:
  (*i*) Lignocaine controls
  (*ii*) Lignocaine + cyclonamine
  (*iii*) Procaine controls
  (*iv*) Procaine + cyclonamine.

Table III shows the grades of bleeding, the mean grade, and its standard error for these five groups. (The standard errors are based on a pooled estimate of variance having 206 degrees of freedom, see appendix Table AI.)

TABLE III
GRADE OF BLEEDING IN FIVE GROUPS OF EYES

Section	Graefe Section	Knife and Scissors Section				Total
Anaesthesia		Lignocaine		Procaine		
Treatment		Control	Cyclonamine	Control	Cyclonamine	
Group No.	1	2 (*i*)	2 (*ii*)	2 (*iii*)	(2 (*iv*)	
Grade of Bleeding 1	12	4	8	13	15	52
2	7	29	30	13	11	90
3	9	23	13	10	3	58
4	2	6	2	2	2	14
5	—	3	1	—	—	4
Total Cases	30	65	54	38	31	218
Mean Grade	2·03	2·62	2·22	2·03	1·74	2·21
Standard Error	0·16	0·11	0·12	0·15	0·16	0·06

(1) *Graefe Section.*—In these cases (13·76 per cent. of the total) it was found that neither cyclonamine nor any of the other variables had a significant effect on bleeding.

(2) *Knife and Scissors Section.*—In this group (86·24 per cent. of the total) two factors were found to affect bleeding independently:

(*a*) Cases receiving retrobulbar procaine 2 per cent. with 1 in 50,000 adrenaline had an average of 0·54 ± 0·13 of a grade less bleeding than those injected with lignocaine 2 per cent. with 1 in 80,000 adrenaline.

(*b*) Cyclonamine was found to reduce bleeding by 0·35 ± 0·13 of a grade. Both these effects are highly statistically significant.

Table III shows that the bleeding of the Graefe cases (Group 1) is statistically significantly less than the knife and scissor controls receiving lignocaine with the weaker adrenaline (Group 2*i*). This group had the highest bleeding of the knife and scissors cases. In Groups 2*ii*, *iii*, and *iv* this difference is reduced by cyclonamine, or procaine with the stronger adrenaline, which lessened the bleeding. The difference between Group 1 and Groups 2*ii*, *iii*, and *iv* is not statistically significant.

Hyphaema

There is no suggestion in Table I that post-operative hyphaema is associated with the grade of operative bleeding, nor does it appear to be much reduced by cyclonamine. Table IV shows the number and percentage of cases with hyphaema in the five groups of patients identified above. There is no evidence of statistically significant variation in these percentages (χ^2(4 degrees of freedom) = 5·40; 0·3 > P > 0·2).

TABLE IV
DISTRIBUTION OF CASES OF HYPHAEMA

Hyphaema Present	Graefe Section		Knife and Scissors Section								Total	
			Lignocaine				Procaine					
			Control		Cyclonamine		Control		Cyclonamine			
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
No	30	100	58	89·2	52	96·3	36	94·7	28	90·3	204	93·6
Yes	—	—	7	10·8	2	3·7	2	5·3	3	9·7	14	6·4
Total	30	100	65	100	54	100	38	100	31	100	218	100

It is not clear why cyclonamine was found to be effective in knife and scissors sections, and yet of no value with the Graefe sections. A further trial would be necessary to determine whether this result was of importance.

Though incidental to the trial, it is a useful finding that bleeding was reduced significantly in those receiving retrobulbar procaine 2 per cent. with 1 in 50,000 adrenaline as against lignocaine 2 per cent. with 1 in 80,000 adrenaline.

It is noteworthy that, despite haemorrhage reduction in the cyclonamine group, there were still a few cases in the 4+ and 5+ category receiving this drug, and the overall picture of less bleeding on the operating table was not sufficiently striking to be immediately apparent to the operating surgeon.

Larger doses of cyclonamine have been used by many previous workers reporting good results (Stucchi and Nouri, 1962; Vicari, 1963; Canal, 1964; etc.), and it is likely that a heavier dose, such as 500 mg. pre-operatively, is necessary in ophthalmic surgery.

Although there was no significant reduction in post-operative hyphaema in the cyclonamine group, Raby and Coupier (1965) have commented that the effect of cyclonamine on capillary fragility lasts for 2 days and diminishes over 5 to 6 days, which would cover this post-operative period in hospital.

The finding of excellent toleration of cyclonamine is in agreement with previous investigators (Fumeaux, 1961; Müller, 1962; Jichlinski, 1963, etc.).

Summary

A clinical trial of cyclonamine (250 mg. by intramuscular injection) given pre-operatively in cataract surgery is described.

Cyclonamine reduced operative bleeding to a highly statistically significant degree in cases undergoing knife and scissors section, but was not shown to be effective in cases in which a Graefe section was performed.

There was no significant difference in post-operative hyphaema between the cyclonamine and control groups.

It is suggested that a more satisfactory effect may be obtainable with a heavier dose of the drug.

There were two incidental but statistically significant findings:

(*a*) Knife and scissors cases receiving retrobulbar procaine 2 per cent. with 1 in 50,000 adrenaline had less operative bleeding than those injected with lignocaine 2 per cent. with 1 in 80,000 adrenaline;

(*b*) Cases in which the Graefe section was used bled less at operation than knife and scissors cases receiving retrobulbar lignocaine with adrenaline in the control group, but were not significantly different from the other groups.

Cyclonamine was well tolerated throughout.

We are indebted to the staff of the St. John Ophthalmic Hospital, and in particular the ward sisters and Hasan Abu Teen for their helpful co-operation in this trial.

We should also like to thank Om Laboratories, Geneva, for supplying the Dicynone ampoules, and the Cambridge Mathematical Laboratory for the use of their electronic computer.

The proposed international name for cyclonamine is now "cyclonamin".

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APPENDIX

Statistical Analysis

It was thought that the degree of bleeding might be influenced by:

(1) Age
(2) Sex
(3) Retrobulbar injection—(lignocaine or procaine)
(4) Operative technique—(von Graefe knife or knife and scissors)
(5) Iridectomy (peripheral or broad)
(6) Treatment (control or cyclonamine)

Multiple regression analysis was carried out as described by Rushton (1951), in which we attempted to explain the grade of bleeding, considered as a linear scale, in terms of these factors in the order listed. After trying to explain the bleeding in terms of these main effects, the possibility that the treatment effect might be influenced by factors 1 to 5 was considered, *i.e.* sum of squares for interactions of variables 1 and 6, 2 and 6, 3 and 6, 4 and 6, and 5 and 6 was examined. The results are shown in Table AI.

TABLE AI

ANALYSIS OF THE EFFECT OF TREATMENT, FIVE OTHER FACTORS, AND THEIR INTERACTIONS WITH TREATMENT, ON THE GRADE OF BLEEDING

Source of Variation		Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio	Significance
Main Effects	Age	0·915	1	0·915	1·123	Cannot be validly tested because of significant effect below
	Sex after Age	1·142	1	1·142	1·400	
	Retrobulbar injection	9·792	1	9·792	12·007	
	Type of Section	4·247	1	4·247	5·208	
	Iridectomy	0·097	1	0·097	0·119	
	Treatment	2·980	1	2·980	3·654	
	after above factors					
Interactions: Treatment	× Age	0·145	1	0·145	0·178	
	× Sex	1·094	1	1·094	1·342	
	× Injection	0·031	1	0·031	0·038	
	× Section	3·824	1	3·824	4·689	0·05 > P > 0·01
	× Iridectomy	0·024	1	0·024	0·029	Insignificant
	after above factors					
Residual		168·001	206	0·816		
Total		192·294	217			

The significant interaction indicates that the response to treatment was different in cases in which the von Graefe knife was used from that in the remainder. The data were therefore split on Variable 4, and the analysis was repeated. The results were as follows:

(*a*) *Graefe Cases*

Among the thirty cases in which the von Graefe knife was used, neither the treatment nor any of the other variables had any significant effect on bleeding. The largest effect was that of sex. Eight of the thirteen males in this group had Grade 1 bleeding only, and none had more than Grade 3 bleeding. More bleeding occurred among the seventeen females but the difference was not statistically significant, $0{\cdot}1 > P > 0{\cdot}05$. Cyclonamine appeared to *increase* bleeding by $0{\cdot}56 \pm 0{\cdot}38$ of a grade, but with so few cases the effect of the drug cannot be said to be known with any certainty.

(*b*) *Knife and Scissors Cases*

In the remaining 178 knife and scissors cases, two effects stand out and are statistically highly significant (Tables AII and AIII, overleaf). The significant factors are the effect of cyclonamine, which for these cases *reduced* the bleeding by $0{\cdot}35 \pm 0{\cdot}13$ of a grade, and the type of retrobulbar injection. Patients in whom procaine with adrenaline 1 in 50,000 was used had an average $0{\cdot}54 \pm 0{\cdot}13$ of a grade *less* bleeding than those anaesthetized with lignocaine with adrenalin 1 in 80,000. The two effects are virtually independent and no other factors had any appreciable influence on bleeding.

TABLE AII

KNIFE AND SCISSORS CASES ONLY

ANALYSIS OF THE EFFECT OF TREATMENT, FOUR OTHER FACTORS, AND THEIR INTERACTIONS, ON THE GRADE OF BLEEDING

Source of Variation		Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio	Significance
Main Effects	Age	0·685	1	0·685	0·858	Cannot be validly tested because of significant effect below
	Sex after Age	0·224	1	0·224	0·281	
	Retrobulbar Injection	12·818	1	12·818	16·066	
	Iridectomy	0·014	1	0·014	0·018	
	Treatment	5·650	1	5·650	7·082	0·01 > P > 0·001
	after above factors					
Interactions: Treatment	× Age	0·124	1	0·124	0·155	P > 0·5
	× Sex	0·390	1	0·390	0·489	P > 0·5
	× Injection	0·117	1	0·117	0·147	P > 0·5
	× Iridectomy	0·191	1	0·191	0·239	P > 0·5
	after above factors					
Residual		142·016	178	0·798		
Total		162·229	187			

TABLE AIII

KNIFE AND SCISSORS CASES ONLY

SECOND ANALYSIS OF THE EFFECTS OF TREATMENT AND FOUR OTHER FACTORS ON THE GRADE OF BLEEDING

Source of Variation		Sum of Squares	Degrees of Freedom	Mean Square	Variance Ratio	Significance
Main Effects	Treatment	5·737	1	5·737	7·308	0·01 > P > 0·001 (from Table IV)
	Retrobulbar injection after treatment	12·736	1	12·736	16·224	0·001 > P
	Age	0·620	1	0·620	0·789	P > 0·5
	Sex	0·239	1	0·239	0·305	P > 0·5
	Iridectomy	0·058	1	0·058	0·074	P > 0·5
	after above factors					
Residual		142·838	182	0·785		
Total		162·229	187			

Validity of Model

The validity of the mathematical model for the statistical analysis may be illustrated as follows. Consider Groups 2*i* and 2*iv* shown in Table III of the paper. The estimated difference in the mean bleeding between these groups is 0·89 of a grade. The model for the analysis assumes that the grade of bleeding is a linear scale and that the effects of the treatments apply equally to all the patients.* Consequently, when comparing Groups 2*i* and 2*iv*, one would expect 89 per cent. of patients in Group 2*i* with Grade 5 bleeding to have moved down into Grade 4 when treated with procaine and cyclonamine. Similarly, these two factors should move 89 per cent. of Group 2*i* patients with Grade 4 bleeding down into Grade 3 and so on. Patients in Grade 1 cannot move down any further. Thus, from the effects of treatment and the distribution of cases in Group 2*i*, an expected distribution of cases in Group 2*iv* may be derived. This is shown in Table AIV together with the observed distribution. Observed and expected distributions could scarcely be more similar, showing that the model fits the data well.

TABLE AIV

OBSERVED AND EXPECTED BLEEDING OF KNIFE AND SCISSORS CASES TREATED WITH PROCAINE AND CYCLONAMINE

Grade of Bleeding	No. of Cases	
	Observed	Expected*
1	15	14·3
2	11	11·3
3	3	3·7
4	2	1·6
5	—	0·1
Total	31	31·0

* For method of deriving expected distribution see text.

* It is not necessary to assume normality since analysis of variance is a robust procedure.