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A PROSPECTIVE RANDOMIZED DOUBLE MASKED CONTROLLED CLINICAL TRIAL TO DETERMINE THE EFFICACY OF MULTIPLE DROP CENTBUCRIDINE AS AN OCULAR SURFACE ANAESTHETIC

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Abstract : In this study, the ocular surface anaesthetic and analgesic efficacies of 0.5% and 1% centbucridine both in saline were compared with 4% lignocaine drops in distilled water in normal healthy volunteers divided into three equal groups. In 99 healthy eyes, keeping one eye as an unanaesthetized control, one drop of any of the above three coded drugs was instilled in the contralateral eye, followed by one more drop of the same drug in the same eye after 3 minutes. The oneset of anaesthesia, achievement and duration of peak activity, total duration of action, the depth of analgesia, and period of burning sensation were all noted in this double-masked randomized controlled trial with the various drug solutions. Total peak duration of anaesthetic as well as analgesic effects in the 99 healthy normal eyes were found to be the highest with centbucridine 1%, followed by 4% lignocaine and 0.5% centbucridine respectively.

Key words : centbucridine lignocaine (lidocaine) local anaesthetics surface anaesthesia infiltration anaesthesia multiple drops opthalmic anaesthesia

INTRODUCTION

Various drugs are presently available for local ocular surface anaesthesia. However, none of these are free from side effects, or really the ideal local anaesthetic. An ideal anaesthetic should include the ability to be used both for topical & infiltration

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anaesthesia, adequate duration of action and freedom from side effect. However, none of the presently available anaesthetic agents have these. Hence, there is a constant need and search for suitably effective yet safe newer local anaesthetic agents which can be used both topically as well as in an injectable form. Centbucridine, a polymethyl quinocompound, is a newer local anaesthetic of the amide group, first synthesized and developed indigenously by the Central Drug Research Institute (CDRI) at Lucknow, India (1). Various experimental and clinical trials carried out with this compound demonstrated its efficacy as a surface anaesthetic (2, 3). It has been shown to have a wide margin of safety based on pharmacological (4), and chronic toxicity (5), teratogenicity (6), neurotoxicity (7) genotoxicity (8) and clinical pharmacology studies (3).

Our previous experience with a single drop study (9), prompted us to continue with this multiple drop instillation study, to enable us to understand more about the potential use of centbucridine as a local anaesthetic in clinical practice.

METHODS

Ninety-nine healthy volunteers were enrolled, 33 in each group, divided in a computer generated randomized manner (Table I). A brief medical history was noted to rule out local and systemic factors which could affect corneal sensations, subject response or the Bell's phenomenon, such as diabetes, leprosy, neurological and endocrinal disorders; use of drugs like sedatives, tranquillizers and alcohol; contact lens wearing, previous viral keratitis, trachoma and other corneal diseases, dry eyes, glaucoma, thyroid ophthalmopathy; and use of local medications (especially timolol maleate). A complete ocular assessment including intraocular pressure measurements, fundus examination and slit lamp biomicroscopy was done. Written informed consents were taken from all the subjects, and Institutional Ethics Committee's approval was obtained. Centbucridine hydrochloride powder (Unichem Labs., Mumbai) was dissolved in normal saline and was prepared in concentrations of 0.5% and 1% (10). These, and similar colourless 4% lignocaine hydrochloride (available as Xylocaine® from Astra IDL, Bangalore in distilled water) were dispensed in identical looking colourless vials to be used in a coded manner as a surface anaesthetic agent. The code was kept sealed with one of us (NRB). In one eye of each volunteer in a group, one drop of the coded drug was instilled in a double masked manner, followed by one more drop of the same drug in the same eye after 3 minutes. The contralateral eye with no drops served as an unanaesthetized control.

Testing for corneal surface anaesthesia: The corneal tactile sensations in the study eye were checked with a fine cotton wisp brought in from the lateral side and not touching the eye lashes so as to avoid the unwanted corneal blink reflex (9). Starting one minute after the 2nd instillation of the coded drug, the tactile sensation was checked over the central 3 mm of cornea to note the earliest onset of corneal anaesthesia. After each 5 minute interval, the tactile sensation was tested at three pre-determined sites: central 3 mm of cornea,

temporal peripheral cornea 1 mm inside the limbus, and temporal conjunctiva 3 mm outside the limbus. As before (9), the objective and subjective responses of the cornea and conjunctiva were graded based on the degree of induced blink and Bell's phenomenon as noted by us, as well as the subjective feeling reported by the patients. Bell's phenomenon is the physiological response of eyelid closure being concomitantly associated with reflex up and out movement of the eyeballs.

Testing for ocular surface analgesia: In the study eye, the temporal conjunctiva 5 mm from limbus was clasped with a non-toothed forceps at 5 minute intervals to obtain the ocular surface analgesic action, similar to earlier reports by us (9) and by Linn and Vey (11). The responses obtained were graded from the subjective responses of painful to slight discomfort, to no pain or discomfort. Observations were recorded according to code of the drug, and entered into Excel software for statistical analysis. One-way analysis of variance (ANOVA) was applied to detect the statistically significant differences between the mean values (9). In case of significant difference shown by ANOVA, post-analysis variance (i.e., multiple range test) was applied to detect the statistically significant differences between various pairs of group means (12). The analysis was done using STATA 6.0 intercooled version package. After this, vials were decoded and results interpreted.

RESULTS

The total peak duration of anaesthetic effect (Table I) was found to be significantly highest with centbucridine hydrochloride 1% in saline, followed by 4% lignocaine hydrochloride in water and 0.5% centbucridine hydrochloride in saline respectively (Table I). Similarly, total duration of anaesthetic effect was found to be highest with centbucridine 1%, far more than the duration of that with lignocaine 4% ($P<0.05$) and centbucridine 0.5% ($P<0.001$). Analgesic effects (both peak and total durations) were also found to be highest with centbucridine 1% followed by lignocaine 4% and centbucridine 0.5% (Table I), though not as significantly so. A mild burning sensation was experienced

TABLE I: Ocular surface anaesthetic efficacies of multiple drops of 1.0 and 0.5% centbucridine hydrochloride and lignocaine hydrochloride 4% (N=99 eyes).

Name of drugs	*Anaesthesia*		*Analgesia*	
	Total peak duration (min)	*Total duration (min)*	*Total peak duration (min)*	*Total duration (min)*
Drug A (1% Centbucridine n=33 eyes)	37.43±10.39[a]	58.43±11.0[a]	15.29±8.99	29.29±8.50
Drug B (0.5% Centbucridine n=33 eyes)	14.85±9.48[b]	32.29±8.69[b]	8.79±8.75	22.12±10.46
Drug C (4% Lignocaine n=33 eyes)	19.03±5.23[c]	35.16±4.18[c]	12.10±6.55[c]	28.26±5.14
A vs B	[a]P<0.001	[a]P<0.001	NS	NS
A vs C	[c]P<0.001	[c]P<0.001	NS	NS
B vs C	[b]P<0.01	NS	[b]P<0.05	NS

All results are Mean±SD.

for a maximum of two minutes with all the three drugs. Centbucridine in saline was better tolerated than in water (10). No other side effects were encountered during the study period in any of the three groups.

DISCUSSION

Lignocaine (an amide) has been the time-honoured local anaesthetic since the 1940s, both for topical and infiltration anaesthesia. Centbucridine hydrochloride (also an amide) was synthesized only in 1975 (1) and its efficacy reported occasionally since then. Though various studies have proved it to be an effective local anaesthetic agent (9, 13-15), no further approaches had been made in a practical manner so that it could be more widely used as a topical anaesthetic, at least not in ophthalmology. A discouraging report (16) in 1977 with injectable 2% lignocaine as compared to 0.25% centbucridine in a relatively obscure local publication did not help to generate wider interest in this newer compound, except maybe to help us try the higher 0.5% concentration for injectable, and 1% for topical anaesthesia. Our initial experiences with single drop instillation of centbucridine (9), prompted us to evaluate its multiple drop effect in this current study.

The earlier single drop study (9) had shown that centbucridine hydrochloride can be used successfully as a topical anaesthetic drug. Our subsequent study (10) of pH and osmolarity with Centbucridine proved that by altering its vehicle from distilled water to saline, the efficacy of the drug could be significantly improved, and also side effects like burning sensation could be minimized (10).

In our current multiple drop study, we found that centbucridine hydrochloride in saline in 1% concentration gave the maximum analgesic and anaesthetic effects, though the duration of analgesia was lesser than that of the anaesthesia. The total duration of anaesthesia obtained with centbucridine hydrochloride 1% (i.e., 58.43±11.0 min) may be considered as an optimal period for any local anaesthetic procedure in opthalmology. Most of the routine surgeries, even intraocular (like phacoemulsification), can be performed during this time period by most ophthalmic surgeons.

The encouraging results of our earlier single drop study (9) coupled with the current experience of this present study have encouraged us for further clinical evaluations of centbucridine, including an extensive clinical trial on different minor ophthalmic procedures requiring either topical centbucridine alone or along with injectable centbucridine anaesthesia also wherever necessary.

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