DISCUSSION
DISCUSSION

Intravenous administration of a local analgesic drug, to provide pain relief during surgery, on the limb, although theoretically, a good and sure technique as compared to the cumbersome and unpredictable regional blocks, yet, has not very much enjoyed the acceptance of modern anaesthesiologists, largely because of the toxicity reactions of the drugs in use. Most of these drugs have the principal disadvantage of being central nervous and cardiovascular system depressants and these two singled out mar their efficacy as intravenous regional analgesics.

A drug devoid of such toxicity reactions would definitely prove a boon to the simple and effective technique, particularly for an anaesthetist working under field conditions.

CENTBUCRIDINE, a polymethylene quinoline derivative, which shows potent and reversible local anaesthetic activity in animals and man, both by infiltration and topical application (Patnaik, G.K., et al, 1982), as well as by the intravenous administration (Suri, et al, 1983), claims an upper hand over its other counterparts firstly, because of its central nervous system stimulant action and secondly, due to its cardiovascular stabilising property. It therefore merits a trial as an agent for intravenous regional analgesia.

The present study, on 60 adult patients, was done
to establish the efficacy of centbucridine as an intra-
venous regional analgesic. This being an almost original
work, is devoid of much literature to support our results,
except that of Suri, et al, (1983), who maintain the drug
to be very potent and effective, more than the conventi-
onal lignocaine et al.

The subjects for this study were 48 males and 12
females ranging between 11-70 yrs. of age, undergoing
both planned (33) and emergency (27) operations (Tables
I & II). Children were excluded from the study as they
are less co-operative and donot appreciate the idea of
a needle being plunged into their arms or feet. Most of
the other workers have also excluded children below the
age of 10 yrs. for the same reason, (Sorbie & Chacha,

The site of operation in this technique could only
be upto the lower one third of the arm or thigh, as the
presence of a continuous and uninterrupted tourniquet
is a must, which would therefore hinder with the surgi-
cal procedures if applied for surgeries on arm or thigh.

Premedication of any sort was avoided in all but
few (2) emergency cases, where because of the lesion the
patients had pain, rendering them restless and uncoo-
perative. Assurance, reassurance and explanation of the tech-
nique proved sufficient for the patients to accept the
procedure. Premedication was avoided for the fact that
it would, firstly mask the effect of drug thereby giving false results and secondly it would delay the stay of patients in the hospital. There has been a general agreement, about the avoidance of premedication, by most workers who have opined that sedative premedication would be detrimental to the rapid recovery from the effects of anaesthesia (Sadove, et al, 1952, and COX, JMR 1964).

As far as sensitivity to the drug is concerned, Centbucridine, after extensive laboratory and clinical trials, has not been found to produce any hypersensitivity reaction, on the contrary it has been shown to carry antihistaminic property, by way of its antagonism of the depressor response to histamine as also blockade of the H₁ histamine receptor in the cardiovascular system and guinea pig ileum (Patnaik, G.K. and Dhawan, B.N., 1982). Sensitivity to local analgesic drugs, in general, is also not very common and to quote Moore and Bridenbaugh (1962), "In less than 2% of cases in whom systemic symptoms arise after the administration of a local analgesic, can a true allergy to the drug be imputed."

The use of single tourniquet in the past always had the disadvantage of tourniquet discomfort and pain during the procedure and has therefore discredited its popularity until, Morrison, in 1931, advocated the use of double cuff tourniquet, which was adopted in clinical practice by Bell, et al, (1963), and Adams, et al, (1964), whereby they reported minimum such discomfort. With the
same aim it was decided to use double cuff tourniquet in our series in all cases, with quite encouraging results.

To achieve uniform and complete spread of the drug the veins were perforated in the distal part of the extremity (dorsum of the hand/foot), as proximal injection would give incomplete effect, because of the powerful venous valves obstructing downward flow of the drug (Sorbie and Chacha, 1965). One of the cases however required venous section because of the inaccessible veins, which again was performed as distal as possible.

Colbern, E.C., (1970), discouraged the use of Esmarch's bandage, which was till then the most popular method of exsanguination and reasoned that gravitational method is equally as effective and avoids the problem of needle dislodgement and pain during application of the bandage. Same principle adopted in our series showed that gravitational drainage in no way hampers the spread of the drug and uniformity of analgesia. On the other hand it produced satisfactorily dry operative field with minimum blood loss.

**Dose and concentration of the drug:**

Depending upon the concentration of the drug the patients were divided into four groups of 15 each (Table III). The concentrations used were .25, .3, .35 and .4%. In contrast Suri, et al, (1983), used .25, .35 and .5% concentration. On the other hand most of the other drugs
were used in comparatively higher concentrations to get an equal response. Sorbie & Ghacha (1965) and majority of other workers have used lignocaine in .5% concentration while Dawkins, et al, (1964), used it in 1% concentration.

Prilocaine has mostly been used in .5% concentration (Kerr, J.H. 1967), and Dunbar & Mazze, 1967), but concentration as high as 2% have also been administered (Hooper, R.L., 1964).

Chloroprocaine in a concentration of 2% has been recommended (Dickler, et al, 1965). Only bupivacaine has been used in low concentration i.e. .25% (Moore, DC and Bridenbaugh, L.D., 1971).

Differing concentrations used in our series, were to establish an optimal concentration of centbucridine which could give adequate analgesia with minimum or no toxic effects, when administered through the vein.

On an average the volume required in each case ranged between 30-45 ml. for the upper extremity and 56-77 ml. for the lower extremity (Table IV). Suri, et al, while working on the upper limb alone have recommended average volume of 35 ml. for the extremity. The volume used were inversely proportional to the concentration of the drug and was so arranged that the dose in mg remained almost the same in every case i.e. between 100-135 mg. for the upper extremity and
190-240 mg for the lower extremity. In contrast the doses required with other local analgesics are comparatively very high (Lignocaine 200-400 mg, Chloroprocaine upto 800 mg, Prilocaine 200-800 mg), with the exception of bupivacaine which is recommended in almost similar quantity i.e. 75-150 mg.

Time of onset of Analgesia:

Lower the concentration of the drug more was the time required for the onset of its action. In group I the patients required almost 5 minutes for the onset of action while in group IV sensory loss was observed in 1-2 minutes only while motor loss was seen in 2-3 minutes (Table V). In striking contradiction to our findings Suri, et al, (1983), observed almost equal time of onset of analgesia in all groups and have found that it required about 5 minutes for the sensory loss and 6 minutes for the motor loss.

The time of onset for other local analgesics as observed by other workers shows that minimum time is taken by lignocaine i.e. 3-5 minutes (Atkinson, et al, 1965), and maximum time of 11 minutes is taken by bupivacaine (Moore & Bridenbaugh, et al, 1971). Centbucridine so far takes minimum time for the production of adequate analgesia.

Effect of Analgesia:

The drug is found to produce substantially good
analgesia when used in concentration, more than .3%
As shown in tables VI-a to -d, it can be found that
the degree of analgesia was excellent/good in 93% and
100% cases with .35 and .4% concentrations respectively.

On the other hand it was 26.66% with .25% concentra-
tion and about 80% with .3% concentration. Both these
later groups exhibited rather unsatisfactory quality, in
73% and 20% cases respectively. It can therefore be in-
ferred that concentrationsabove .3% are better suited for
surgical manoeuvres.

Suri, et al (1983), in agreement to our findings
also discard .25% concentration and suggest .35% as the
minimum required concentration for the effective anal-
gesia. The effect of analgesia with lignocaine has ran-
ged between 70-96% with minimum advisable concentration
(Holmes, C. Mck 70%) Sorbie and Chacha 85%, Schiller,
M.G. 91% and Dunbar, et al, 96%), Dawkins using concen-
tration as higher as 1% lignocaine could get only 95%
good results while on the other hand a concentration as
low as .4% in our series exhibited 100% response.
Injection tourniquet release time interval:

In none of the cases, tourniquet was released ear-
lier than 45 minutes, no matter howsoever short the ope-
rate procedure had been.

Bier, (1908), stated that toxic reactions appear
to be more common when the injection release time inter-
val is less than 25 minutes. Morrison (1931), recommended
the time interval to be 30 minutes. Dawkins, et al, (1964), in their series had the time interval as low as 10 minutes, but the quantity and concentration of the drug also had been higher, hence it becomes difficult to explain which of the two factors are to be blamed for the incidence of toxic reactions in their series, as according to Tucker & Boas, 1971, "Peak levels after cuff release were inversely proportional to the tourniquet application time, they also tended to be lower (by about 40%) when the same dose was given in .5% instead of 1% solution."

The tourniquet was not deflated in a single jerk but it was cycled as suggested by Colbern, E. C., (1970), deflating the cuff for 5 seconds and then reinflating for 45 seconds and the cycle was repeated 5-6 times before finally removing the tourniquet.

In every cases tourniquet was kept in place till the end of surgery and was then deflated. This was done to be sure that effect does not diminish with the release of tourniquet.

**Duration of Analgesia:**

One of the most striking features of the technique is that the duration of analgesia lasts as long as the tourniquet cuff remains inflated, provided of course, the drug effect has set in, as observed by Holmes, C. Mck., 1963, Hooper, R. L., 1965, Dickler, et al, (965), and Moore and Bridenbaugh, 1971.
In agreement to the above findings table VII shows that duration of analgesia in groups III and IV was complete and uniform throughout the inflation time, thereby it started diminishing. Average duration in those two groups was 83.4 minutes and 86.6 minutes respectively. On the other hand group I and II with their respective duration of 31 minutes and 68.26 minutes, showed diminuation of analgesia even before the deflation of tourniquet as evidenced by the prolonged inflation time and supplementation of general anaesthesia in these cases.

Suri, et al, (1963) with a short inflation period of 20 minutes, evidenced a very long duration of analgesia in volunteers receiving 35% concentration solution. They achieved good sensory and motor loss for about 3-6 hrs. They however agree with us that 0.25% solution had almost equal duration of action 37 minutes. In striking contradiction to their findings the cases in our series showed that effect started diminishing in 5-10 minutes in groups III & IV with the complete return of sensation within 17 and 27 minutes respectively, after deflation of the tourniquet.

Holmes, (1963), found that it took 5-10 minutes for the return of sensation after lignocaine, and similarly 10-15 minutes after chlorprocaine(Dickler, et al, 1965), Hooper, however showed a varying period of 1-90 minutes for re-establishment of sensation after intravenous regional prilocaine.
The longest post-deflation analgesia observed so far was with bupivacaine which took on an average 163 minutes for the return of complete sensation, with the effect starting to diminish at 27th minute of release of tourniquet.

This early diminution of effect could well be explained that with the re-establishment of circulation the drug is washed off from the still disputed site of its action. (Sorbie and Chacha, 1965), proving therefore that the drug acts most probably at the nerve terminals instead of the nerve trunks (Fleming, et al, 1966).

The supplementation of anaesthesia with N\textsubscript{2}O + O\textsubscript{2} + trilene/halothane or N\textsubscript{2}O + O\textsubscript{2} with Pentazocine (30mg)+ Diazepam (10 mg) was required in maximum number of cases 53.3% in group I. In groups III and IV only 6.6% cases, for each, required supplementation in the form of either pentazocine (30 mg) or Diazepam (10 mg) to alleviate tourniquet discomfort in the later part of the procedure (Table \textbf{X}).

**CARDIOVASCULAR AND RESPIRATORY CHANGES:**

Kennedy, et al, (1965), using lignocaine observed a fall, by 10 beats per minute in the pulse rate in 15% of their cases, after the release of tourniquet. The blood pressure also showed hypotensive trend with no effect on the respiration. Prilocaine however produced a stable cardiovascular and respiratory systems (Hooper, R.L. 1965). Bupivacaine on the contrary produced hypotension
as observed by Moore and Bridenbaugh, (1971).

Centbucridine has been found to produce a near perfect cardiovascular stability both during and after the technique. A concentration dependent marginal fall in pulse rate and insignificant rise in blood pressure were features to be noted (Table IX a-d). The changes were more evidenced after the release of tourniquet. Continuous E.C.G. monitoring, throughout the procedure and even in the post operative period, showed no evidence of any abnormality in the cardiac function, proving therefore, that the drug, with remarkable cardiovascular stability, has a merited use in poor risk patients.

The rise in blood pressure however can be attributed to vasopressor and antihistaminic property of the drug coupled with the feeling of pain as a result of an early return of sensations. Suri et al, (1983), also prove, on experimental and human trials that the drug no doubt produces a near perfect stability of the heart and general circulation.

The respiratory system however showed a significant rise in the rate by 1-4 breaths per minute, which was directly proportional to the concentration of the drug used. The depth of respiration remained adequate with no evidence of insufficiency. The central nervous system stimulant action of the drug along with peripheral stimuli arising from the site of operation can well be attributed to this response.
Incidence of toxicity:

A wide variety of toxic reactions have been described with the drugs, so far conventionally used, in this technique. Kennedy et al. (1965), using lignocaine found vertigo, complete loss of consciousness, atrial and ventricular extrasystole and sinus bradycardia etc. Harris, et al., found light headedness, sense of detachment and muscular twitchings. Dunbar, et al., in addition to some of the above mentioned toxicity reactions observed convulsions and blurred vision. Cox. J.M.R., noticed tinnitus and paraesthesia in tongue.


Prilocaine is responsible for the production of methaemoglobinemia in significant number of cases (Harris, et al., 1965, Daly, et al., 1969, Dunbar and Mazze, (1967).

On the contrary ceftraxidine has been found to produce only minor toxicity reactions like nausea and vomiting, restlessness, facial flushing, drowsiness and venous thrombosis (Table 11). This again was found to be concentration dependent, showing the maximum incidence in group IV and minimum in group I. In group I only one patient (6.66%) was observed to be restless after the release of tourniquet, which was controlled by injection diazepam (10mg) and O2 in halation. In group III, 7 out
of 15 cases showed minor reactions in the form of nausea and vomiting (4 cases, 26.66%), restlessness (2 cases, 13.33%) and facial flushing (1 case, 6.66%). Maximum incidence of toxicity was observed in group IV where almost 93.33% of the cases showed incidence of minor/major toxicity. Major toxicity was observed only in group IV in the form of venous thrombosis (one case) and gangrene of the lower extremity (one case). The cause of gangrene well could be, prolonged intense vasoconstriction as a result of high concentration of the drug in a patient who was grossly anaemic and hypertensive. The limb which was already exposed to anaemic hypoxia and high blood flow rates as a result of hypertension, naturally does not withstand tourniquet for such long a time as 105 minutes in this case. This tourniquet time in itself, which was already more than the recommended time of 90 minutes for a normal limb, can lead to gangrene in an already predisposed limb.

Suri, et al. (1963), observed minor toxicity reactions with .35% and .5% concentration of the drug in the form of emesis, restlessness, facial flushing, drowsiness and localised burning sensations and among major toxicity reactions they found that drug produced venous thrombosis in 2 cases where .5% concentration was used.

When asked, on the completion of the procedure,
about the preference of the technique, as compared to general anaesthesia, most of the patients (45, 76.66%) preferred the technique over general anaesthesia while 15% of the cases thought that later would have been better. About 8% patients were of the view that either of the technique was equally good. (Table XII).

On a review of the above findings it can well be maintained that there is uncontroversial evidence that intravenous regional centbucridine provides a uniform and adequate analgesia and anaesthesia in majority of the cases undergoing surgery under the technique. The optimal concentration as evidenced by the above findings can be .35%, as this concentration provides the best results, a very suitable operating condition and has comparatively low incidence of toxic reactions.

On the contrary although toxicity reactions are much less with .25% and .3% concentrations, but the analgesia produced is either incomplete or absent in majority of the cases, moreover the duration of effect is also very short and the patients required either repeat injection of the drug or supplementation by general anaesthetics. .4% concentration on the other hand no doubt produces 100% results but has the disadvantage of producing a very high (93%) incidence of toxicity reactions and is therefore not suitable.