ERGOMETRINE WITH HYALURONIDASE: SPEED OF ACTION

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Intravenous ergometrine given at the crowning of the foetal head or with the delivery of the anterior shoulder is a most effective means of expediting delivery of the placenta and preventing post-partum haemorrhage. This procedure was first introduced by Davis, of Chicago, in 1940. Lister (1950), in Liverpool, and Martin and Dumoulin (1953), of University College Hospital, have demonstrated its efficacy in well-planned clinical trials, and the method is now firmly established in obstetric practice.

Although the technique is widely used by obstetricians, it has one great drawback in that midwives, who in this country conduct the majority of public hospital and domiciliary deliveries, are denied its use because normally they are not trained to give intravenous injections. For this reason a simplified method is often used in which ergometrine is given by *intramuscular* injection instead of by the original intravenous route (Flew, 1947; Daley, 1951). Although some of the speed and reliability of the intravenous method is sacrificed in this modification the much greater general applicability of the intramuscular injection has led to its general acceptance.

In an attempt to enhance the value of the intramuscular method still further, Kimbell (1954) has advised that hyaluronidase ("hyalase," "rondase," "wydase") be added to the ergometrine injection. The rationale of this method is that hyaluronidase, acting as

a "spreading factor," aids absorption of the drug from the injection site and so shortens the latent period inherent in all intramuscular methods. Kimbell has published results that are superior to those obtained by the plain intramuscular method and even approach the efficiency of the original intravenous technique. The merits of the ergometrine-with-hyaluronidase method justify, he believes, its routine adoption by midwives in their unsupervised practice.

Details of Investigations. The External Recording Method was used in the First Four Days of the Puerperium, the Intra-uterine Balloon Method Thereafter

Case No.	Day of Puerperium	Injection Given		Time of Onset of Oxytocic Response
		Ergometrine	Hyaluronidase	
First Control Series				
1	8th	0.5 mg. I.M.	—	3' 50"
2	5th	0.5 " "	—	5' 0"
3	7th	0.5 " "	—	7' 10"
4	2nd	0.5 " "	—	7' 10"
5	2nd	0.5 " "	—	5' 40"
6	6th	0.5 " "	—	11' 40"
7	3rd	0.5 " "	—	7' 10"
8	2nd	0.5 " "	—	4' 20"
9	5th	0.5 " "	—	7' 10"
10	3rd	0.5 " "	—	5' 0"
11	2nd	0.5 " "	—	10' 20"
12	3rd	0.5 " "	—	9' 30"
Mean = 7' 0" (S.D. = 2' 33")*				
Main Series				
13	2nd	0.5 " "	330 i.u.	4' 0"
14	3rd	0.5 " "	1,000 "	3' 20"
15	3rd	0.5 " "	330 "	5' 30"
16	3rd	0.5 " "	1,500 "	6' 20"
17	3rd	0.5 " "	1,500 "	5' 0"
18	3rd	0.5 " "	1,500 "	4' 0"
19	2nd	0.5 " "	1,500 "	5' 20"
20	3rd	0.5 " "	1,500 "	5' 20"
21	3rd	0.5 " "	1,500 "	5' 20"
22	6th	0.5 " "	1,500 "	3' 20"
23	2nd	0.5 " "	1,500 "	5' 20"
24	2nd	0.5 " "	1,500 "	4' 30"
Mean = 4' 47" (S.D. = 56")*				
Second Control Series				
25	4th	0.25 mg. I.V.	—	40"
26	2nd	0.25 " "	—	50"
27	2nd	0.25 " "	—	40"
28	2nd	0.5 " "	—	50"
29	2nd	0.5 " "	—	30"
30	2nd	0.25 " "	—	35"
Mean = 41" (S.D. = 8")*				

* Corrected for small series. Standard deviation = $\sqrt{\frac{\sum d^2}{n-1}}$

FIG. 1.—External records comparing speed of action of (a) intravenous ergometrine, (b) intramuscular ergometrine with hyaluronidase, and (c) intramuscular ergometrine without hyaluronidase.

This paper reports exact measurements of the delay between injection and response of (a) intravenous ergometrine, (b) intramuscular ergometrine, and (c) intramuscular hyaluronidase-ergometrine mixture.

Method

Records of uterine contractility were obtained from 30 healthy volunteer patients in the early days of the puerperium either, externally, by the "Oxford" tocograph (Embrey, 1955, 1958) or, internally, by the older intra-uterine balloon method (Moir, 1932a, 1932b). After a suitable control period, 0.5 mg. of ergometrine maleate with added hyaluronidase was given by intramuscular injection to 12 patients (main series), and its effect on uterine contractility recorded graphically. In each case the time

FIG. 2.—Effect of (a) intramuscular ergometrine and (b) intramuscular ergometrine with hyaluronidase as shown by internal recording.

of onset of the oxytocic response was measured accurately for comparison with the two control groups. In one of these (first control series) 12 patients were given ergometrine *without* hyaluronidase intramuscularly; in the other (second control series) six patients received ergometrine by intravenous injection. The table shows dosage and other details.

Results

In all cases the well-known oxytocic response to ergometrine was recorded, the only difference between the various groups tested being the length of the latent period from the moment of injection to the onset of the oxytocic effect. The average times were: intravenous ergometrine, 41 seconds; intramuscular ergometrine with hyaluronidase, 4 minutes 47 seconds; and intramuscular ergometrine without hyaluronidase, 7 minutes.

Examples of records obtained with the external apparatus are shown in Fig. 1, and with the internal balloon method in Fig. 2.

Comment

The studies show that the addition of hyaluronidase to the injection undoubtedly quickens the speed of action of intramuscular ergometrine. The mean figures indicate an approximate gain of two minutes, reducing the latent period from seven minutes to five minutes. Valuable as this gain may be in a particular case, the real merit of the method has to be judged by the degree to which hyaluronidase accelerates the action of intramuscular ergometrine and approximates it to that of the intravenously injected drug. Viewed in this context, it is questionable whether a gain of two minutes is sufficient to justify the use of the ergometrine-hyaluronidase mixture routinely at the end of the second stage of labour. Again, it will be noted that even with the addition of hyaluronidase the intramuscular ergometrine still takes almost five minutes to exert its effect. This is certainly too slow for the treatment of the emergency haemorrhage. It is more than five times slower

than the intravenous injection, which clearly must remain the method of choice in dealing with sudden post-partum haemorrhage. However, for the midwife who normally is not trained to make an intravenous injection, intramuscular ergometrine-with-hyaluronidase may well be worth while in such circumstances, though in practice any advantage may be annulled by the extra time required to prepare the mixed injection.

Another aspect of the matter must be considered. The present work shows that the addition of hyaluronidase confers upon the intramuscular injection of ergometrine a uniformity of action it does not otherwise possess. Without hyaluronidase the latent period before ergometrine takes effect varies considerably, and in some cases there has been a delay as long as 10 or 11 minutes (see Table). Given with hyaluronidase there is good expectation that intramuscular ergometrine will act within five minutes. The longest delay recorded with hyaluronidase in this series has been just over six minutes, which is a distinct improvement on the figures obtained when using the plain intramuscular method. It may be that in this element of uniformity lies the chief merit of the ergometrine-with-hyaluronidase injection. This could help explain the good results obtained by Kimbell in his clinical series, for the use of the hyaluronidase combination avoids the delays that may occur with the plain ergometrine.

While the addition of hyaluronidase slightly increases the speed and uniformity of action of intramuscular ergometrine, it does not follow that the plain intramuscular method is outmoded. Ergometrine alone has some advantages peculiar to itself. It is simple, more quickly prepared, quite efficacious, and better than no method at all. Finally, if midwives are to use ergometrine routinely at the end of the second stage of labour (as distinct from its use in emergency haemorrhage) supervising authorities should not lose sight of the fact that, at present, the addition of hyaluronidase to the injection quadruples the cost.

Summary

The methods of giving ergometrine by (a) intravenous injection, (b) intramuscular injection, and (c) intramuscular injection with added hyaluronidase at crowning of the foetal head, are reviewed and examined.

It is questionable whether the increased speed of action achieved with hyaluronidase added to the intramuscular injection of ergometrine warrants the adoption of the method routinely in the second stage of labour.

REFERENCES

- Daley, D. (1951). *J. Obstet. Gynaec. Brit. Emp.*, 58, 388.
- Davis, M. E. (1940). *Amer. J. Surg.*, 48, 154.
- Embrey, M. P. (1955). *J. Obstet. Gynaec. Brit. Emp.*, 62, 1.
- (1958). *Ibid.*, 65, 200.
- Flew, J. D. S. (1947). *Proc. roy. Soc. Med.*, 40, 370.
- Kimbell, N. (1954). *Brit. med. J.*, 2, 130.
- Lister, U. M. (1950). *J. Obstet. Gynaec. Brit. Emp.*, 57, 210.
- Martin, J. D., and Dumoulin, J. G. (1953). *Brit. med. J.*, 1, 643.
- Moir, J. C. (1932a). *Ibid.*, 1, 1022.
- (1932b). *Ibid.*, 1, 1119.

On June 26 the DUCHESS OF DEVONSHIRE opened a new out-patient department at the Children's Hospital, Sheffield, to replace one which is now too small for its purposes. The new building, costing £110,000, has been insulated so as to lessen noise, and is provided with small "waiting areas" for the clinics instead of the usual large waiting-hall. To please the children, primary colours have been used for the decorating. The department represents the first stage in the development of the hospital.