

SOME STUDIES ON SYNTHETIC OXYTOCIN (SYNTOCINON*)

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Posterior pituitary extracts have been used in obstetrics since long on account of their oxytocic effect. Kamm et al (1928) separated the vasopressor and oxytocic fractions in fairly pure form. Van Dyke and his colleagues obtained a non-crystalline material from posterior pituitary extracts which were protein in nature and had much greater biological activity. Du Vigneaud et al (1953) obtained highly purified preparations of vasopressin and oxytocin from beef pituitaries and established their chemical structure. They showed that each of these hormones contains eight amino-acids, six of which are common to both, and iso-leucine and leucine in oxytocin are replaced by phenylalanine and arginine in vasopressin. The molecular weight of oxytocin is 1007 and that of vasopressin 1084. In 1954, Du Vigneaud was able to synthesise oxytocin and, in 1955, Boissonnas evolved a method for its commercial manufacture. The synthetic oxytocin is put in the market by Sandoz Company under

the trade name of 'Syntocinon'.

With the availability of the oxytocic hormone or fraction in pure form (by synthesis) it became possible to study its effects without contamination of vasopressor fraction. In general, it has been stated that the oxytocin has mainly actions on uterine musculature and mammary gland whereas the vasopressor fraction has vasopressor and anti-diuretic activity.

In the present study effects of syntocinon on the duration of the third stage, third stage bleeding, as also on the blood pressure have been observed under controlled conditions and subjected to statistical analysis. In most of the studies by other workers, specially of the western countries, anaesthesia has been generally used in labour and the effects of syntocinon have naturally been perhaps modified by the different anaesthetising agents employed. In the present study no anaesthesia was employed in labour and therefore it can be surmised that the effects of synthetic oxytocin have been studied without the disturbing influence of anaesthesia.

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* Trade name of the synthetic preparation.

Choice of Subjects

In the present study, 100 cases of normal labour, who came for deli-

very to the K. R. Hospital, were divided into two groups of 50 each. Alternate cases were usually allotted to the two groups. In one group no ecboic drug was employed and the labour was allowed to take a natural course. In the other group 10 units of synthetic oxytocin (Syntocinon) were injected intramuscularly after delivery of the anterior shoulder. Fugo and Dieckmann (1958) also employed syntocinon on the appearance of the anterior shoulder. The two groups have been designated 'normal series' and 'Syntocinon series' respectively.

Methods of Study

In both the series the duration of the third stage was noted accurately and all bleeding of the third stage was collected carefully and measured. The blood pressure of each subject in both the series was recorded at the beginning and then at intervals of 5, 10, 15, 20, 25 and 30 minutes and 1, 2 and 3 hours after the delivery of the anterior shoulder (in the normal series), or after the injection of syntocinon (in the 'Syntocinon series').

Observations and Analysis of Data

I. Break up according to Age Groups.

TABLE 1

Age group	Syntocinon series	Normal series
10 to 20 years	14	12
21 to 30 years	29	33
31 to 40 years	6	5
Above 40 years	1 (42 yrs.)	Nil
Total cases	50	50

II. Parity.

Table 2 gives the parity of the subjects in the two series:—

TABLE 2

Parity	No. in Syntocinon series	No. in normal series
Zero para	15	7
One para	9	9
Two para	7	8
Three para	3	8
Four para	4	5
Five para	5	6
Six para	2	2
Seven para	1	3
Eight para	3	Nil
Nine para	Nil	1
Ten para	Nil	Nil
Over ten para	1	1
Total cases	50	50

III. Duration of Third Stage.

The duration of the third stage of labour in the two series was subjected to statistical analysis and Table 3 gives the results:—

TABLE 3

	Syntocinon series	Normal series
Range of the 3rd stage duration	1 to 15 mts.	3 to 20 mts.
Mean	4.11 mts. (m_1)	5.34 mts. (m_2)
Standard deviation (S.D.)	± 2.19	± 3.09

Standard error of the difference between the two means (S.E.D.M.) .. 0.544

Since $m_2 - m_1$ (1.23) is more than twice (actually 2.26 times) the S.E.D.M. (0.544) it is statistically significant.

From Table 3, it is clear that the third stage of labour is significantly shortened by the use of synthetic oxytocin (syntocinon).

IV. Third Stage Bleeding.

Table 4 gives the data regarding the third stage bleeding and its statistical analysis:—

percentage of the total cases in the series). In the case of rises and falls from the initial blood pressure, the mean change and maximum change were determined and charted as also the number of cases showing significant change (i.e. change of 20 mm. Hg. or more).

Table 5 shows the above data for

TABLE 4

	Syntocinon series	Normal series
Range of the third stage bleeding in ml. ..	0* to 284	0* to 513
Mean	74.22 (m_1)	121.12 (m_2)
Standard deviation (S.D.)	± 59.28	± 102.8

* When the third stage bleeding was less than 3 ml. it is shown as zero.

Standard error of the difference between the two means (S.E.D.M.) .. 16.78

Since $m_2 - m_1$ (46.9) is more than double (actually 2.8 times) the S.E.D.M. (16.78) the difference is statistically SIGNIFICANT.

From the above table it is clear that the third stage bleeding is significantly less in the syntocinon series than in the normal series.

the syntocinon series and Table 6 for the normal series.

V. Effect on Systolic Blood Pressure

The average initial blood pressure (systolic) in the syntocinon series was 124.38 mm. Hg., and in the normal series 119.9 mm. Hg.

In each case, the departure from the initial blood pressure was charted out against a time scale of 5, 10, 15, 20, 25 and 30 minutes and 1, 2 and 3 hours. These timings were from the delivery of the anterior shoulder in the normal series and from the injection of syntocinon in the syntocinon series. The number of cases showing rise, fall or no change in the systolic blood pressure at each time level was worked out in both the series (both absolute number and as

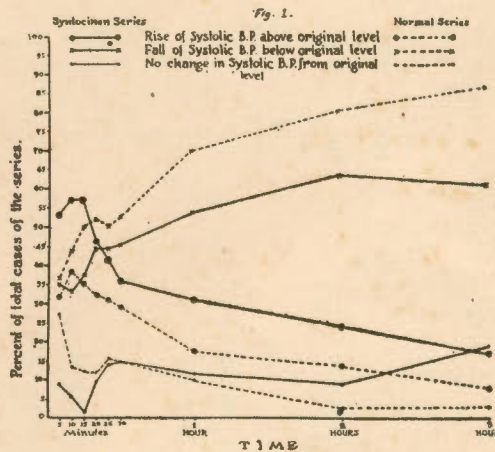


Figure 1 shows graphically the relationship between percentage number of cases showing rises and falls and no change of systolic blood pressure with the time lapse in both the series.

From a perusal of Tables 5 and 6

TABLE 5
Effect on Systolic Blood Pressure in Syntocinon Series
Average initial blood pressure — 124.38 mm.Hg., minimum 104, maximum 160;
140 mm. and over in 5 cases

	5	10	15	20	25	30	1	2	3	Remarks
	Mts.	Mts.	Mts.	Mts.	Mts.	Mts.	Hour	Hours	Hours	
Rise in B.P. {										
Number of* cases	28	30	30	24	21	19	16	12	8	
Per cent	56	60	60	48	42	38	32	24	16	
Average rise, mm.Hg.	8.57	7.16	6.9	7.6	6.9	7.42	10.62	13.83	10.0	
Maximum rise, mm.Hg.	30.0	34.0	32.0	40.0	40.0	40.0	28.0	32.0	20.0	
Rise of 20 mm. or more (No. of cases)	3	1	3	2	1	2	4	3	3	
Fall in B.P. {										
Number of cases	18	17	19	22	22	23	28	33	32	
Per cent	36	34	38	44	44	46	56	66	64	
Average fall, mm.Hg.	9.22	9.76	9.05	7.9	9.18	9.0	10.67	9.48	11.0	
Maximum fall, mm.Hg.	30.0	24.0	22.0	22.0	20.0	21.0	20.0	22.0	22.0	
Fall of 20 mm. or more (No. of cases)	2	1	2	2	3	4	5	6	6	
No change in B.P. {										
Number of cases	4	3	1	4	7	8	6	5	10	
Per cent	8	6	2	8	14	16	12	10	20	

TABLE 6
Effect on Systolic Blood Pressure in Normal Series
Average initial blood pressure — 119.9 mm.Hg., minimum 104 mm.Hg.,
maximum 142 mm.Hg., 140 mm.Hg. and over in 3 cases

	5	10	15	20	25	30	1	2	3	Remarks
	Mts.	Mts.	Mts.	Mts.	Mts.	Mts.	Hour	Hours	Hours	
Rise in B.P. {										
Number of cases	17	20	18	17	16	15	9	7	4	
Per cent	34	40	36	34	32	30	18	14	8	
Average rise in mm.Hg.	6.59	6.3	6.66	6.1	6.06	6.4	9.1	7.1	9.0	
Maximum rise in mm.Hg.	22	22	25	24	18	18	20	20	16	
Rise of 20 mm. or more (No. of cases)	1	1	1	1	0	0	1	1	0	
Fall in B.P. {										
Number of cases	19	23	26	27	26	27	36	42	45	
Per cent	38	46	52	54	52	54	72	84	90	
Average fall in mm.Hg.	4.76	6.26	8.0	7.25	7.15	7.26	8.3	9.66	9.7	
Maximum fall in mm.Hg.	10	20	16	20	20	26	20	20	30	
Fall of 20 mm. or more (No. of cases)	0	1	0	1	1	1	3	2	2	
No change in B.P. {										
Number of cases	14	7	6	6	8	8	5	1	1	
Per cent	28	14	12	12	16	16	10	2	2	

and Fig. 1, some interesting facts emerge.

In the normal series more cases show a fall of systolic blood pressure than a rise throughout the three-hour period. Upto 10 minutes the number of cases showing rise as also of those showing fall in systolic pressure shows rise. Thereafter the number of cases showing rise of pressure goes on declining while that showing a fall goes on increasing.

In the syntocinon series, however, the number of cases showing rise of blood pressure (systolic) is greater than that showing a fall upto 20 minutes. In fact the two curves (Fig. 1) look like mirror images of each other up to the 20 minute period. The number of cases showing rise increases up to 15 minutes and then starts declining, at first steeply and then slowly. The number of cases showing fall decreases up to 10 minutes and then rises sharply up to 20 minutes and gradually thereafter. The two curves cross at the 23rd minute. Moreover the curve showing rise of systolic blood pressure in the syntocinon series runs higher throughout than in that of the normal series. The curve showing fall of systolic blood pressure, however, runs higher in the normal series than in the syntocinon series.

It, therefore, appears that syntocinon (synthetic oxytocin) does have a tendency to increase vasopressor responses and to diminish the vaso-depressor responses. Since, however, after 23 minutes the overall incidence of vasodepressor responses is increasingly higher than the vasopressor responses in the syntocinon series it can be safely surmised that

it (synthetic oxytocin) has no significant vasopressor action. The slightly increased initial incidence of rise in systolic blood pressure is short-lived (up to 20 minutes only).

The incidence in the fall of systolic blood pressure in the syntocinon series was throughout less than in the normal series. Hypotension and myocardial depression, as reported by Mayes and Shearman (1956), i.e. the so-called oxytocin 'shock', was not encountered in the series. Perhaps it was so because the oxytocin was given intramuscularly in this series and not intravenously.

Significant rise in systolic pressure (20 mm. Hg. or above) was observed in more cases in the syntocinon series than in the normal series, e.g. in 4 cases (8%) at one hour period in syntocinon series and in only one case (2%) in normal series.

Significant fall in systolic blood pressure (20 mm. Hg. or more) was again observed more frequently in the syntocinon series (in 6 cases or 12%) than in the normal series (3 cases or 6%) at one hour period.

It, therefore, appears that greater fluctuations (both on the side of increase as also on the side of decrease) in systolic blood pressure occur with syntocinon than without it.

VI. *Effects on Diastolic Blood Pressure*

The average initial diastolic blood pressure in the systocinon series was 81.88 mm. Hg., and in the normal series 78.6 mm. Hg.

In each case the departure from the initial blood pressure (diastolic) was charted out against a time scale of 5, 10, 15, 20, 25, 30 minutes and

1, 2 and 3 hours. These timings were from the delivery of the anterior shoulder in the normal series and from the injection of syntocinon in the 'syntocinon series'. The number of cases showing rise, fall or no change in the diastolic pressure at each time level was worked out in both the series (both as absolute numbers and as percentage of the total cases of the series). In the case of rises and falls of the diastolic pressure the mean change, maximum change as also the number of cases showing significant change (i.e. 20 mm. Hg. or more) was determined and charted.

Table 7 shows the above data for the syntocinon series and Table 8 for the normal series. (See next page).

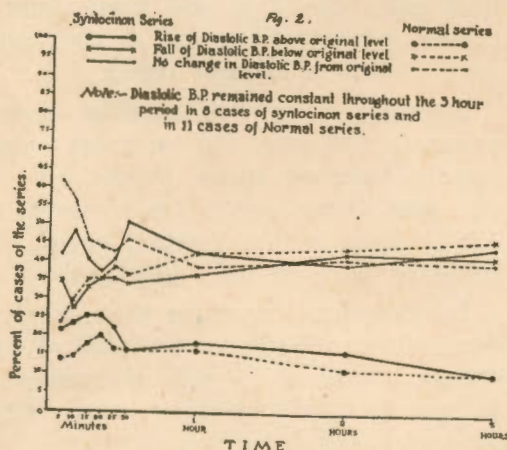


Figure 2 shows graphically the relationship between the percentage number of cases showing rises and falls of diastolic blood pressure and no change with the time lapse in both the series.

Cases having diastolic blood pressure of 90 mm. Hg. or more initially were 23 (46%) in the syntocinon series and 18 (36%) in the normal series.

The number of cases who showed no change at all in their diastolic pressure throughout the three-hour period was 8 (16%) in the syntocinon series and 11 (22%) in the normal series. In case of systolic pressure there was not a single case in either of the two series who showed no change at all throughout the three-hour period. This shows that diastolic blood pressure is more stable than the systolic.

From a perusal of Tables 7 and 8 and Fig. 2, some interesting points emerge.

In both the series almost an equal number of cases shows falls in blood pressure (diastolic) and no change, whereas the number showing rise in diastolic pressure is much less in both the series at all time levels.

The slight initial rise in the incidence of increased diastolic pressure (up to 20 minute period) is a little more marked in the syntocinon series than in the normal one. Thereafter both the curves practically run together with a gradual decline with time.

In general, it can be said that changes in diastolic pressure are less marked than with systolic pressure as the curves showing no change are generally running higher than those showing either rises or falls in the case of diastolic pressure.

Significant (20 mm. or more) rises and falls in diastolic pressure at different time intervals (Tables 7 and 8) are, however, more common in the syntocinon series than in normal series.

VII. Birth of Placenta

In no case, in either of the series, was the placenta retained or needed

TABLE 7

Effect on Diastolic Blood Pressure in Syntocinon Series

Average initial blood pressure — 81.88 mm.Hg., minimum 60 mm.Hg., maximum 110 mm.Hg., 90 mm.Hg. and over in 23 cases, 8 subjects showed no change of B.P. throughout

		5	10	15	20	25	30	1	2	3	Remarks
		Mts.	Mts.	Mts.	Mts.	Mts.	Mts.	Hour	Hours	Hours	
Rise in B.P.	Number of cases	11	12	13	13	11	8	9	8	5	* This change was only in one subject. In others maximum change was 20 mm.Hg.
	Per cent	22	24	26	26	22	16	18	16	10	
	Average rise in mm.Hg.	10.3	11.33	10.77	11.69	10.35	12.0	11.1	13.1	13.6	
	Maximum rise in mm.Hg.	20	20	20	30*	30*	30*	20	30*	20	
Rise of 20 mm. or more (No. of cases)		2	3	3	3	2	3	2	2	1	
Fall in B.P.	Number of cases	18	14	17	18	18	17	19	22	22	
	Per cent	36	28	34	36	36	34	38	44	44	
	Average fall in mm.Hg.	11.1	11.14	9.41	10.77	11.66	10.9	12.4	12.8	12.54	
	Maximum fall in mm.Hg.	20	20	20	20	20	20	20	20	20	
Fall of 20 mm. or more (No. of cases)		4	2	1	1	2	1	4	7	6	
No change in B.P.	Number of cases	21	24	20	19	21	25	22	20	23	
	Per cent	42	48	40	38	42	50	44	40	46	

TABLE 8

Effect on Diastolic Blood Pressure in Normal Series

Average initial blood pressure — 78.6 mm.Hg., minimum 60 mm.Hg., maximum 100 mm.Hg., 90 mm.Hg. or over in 18 cases, no change throughout in 11 cases

		5	10	16	20	25	30	1	2	3	Remarks
		Mts.	Mts.	Mts.	Mts.	Mts.	Mts.	Hour	Hours	Hours	
Rise in blood pressure	Number of cases	7	7	9	10	8	8	8	6	5	
	Per cent	14	14	18	20	16	16	16	12	10	
	Average rise in mm.Hg.	12.0	11.7	11.33	10.2	11.25	11.0	12.0	9.3	9.2	
	Maximum rise in mm.Hg.	20	20	28	28	22	22	20	10	10	
Rise of 20 mm. or more (No. of cases)		1	1	1	1	1	1	2	0	0	
Fall in blood pressure	Number of cases	12	15	18	18	20	19	22	23	25	
	Per cent	24	30	36	36	40	38	44	46	50	
	Average fall in mm.Hg.	11.1	9.46	9.44	10.0	9.9	10.0	11.4	11.13	11.44	
	Maximum fall in mm.Hg.	20	20	20	16	16	20	20	20	20	
Fall of 20 mm. or more (No. of cases)		2	2	1	0	0	1	4	3	3	
No change in blood pressure	Number of cases	31	28	23	22	22	23	20	21	20	
	Per cent	62	56	46	44	44	46	40	42	40	

manual removal.

VIII. *Other Symptoms*

In the syntocinon series, two cases complained of severe pain in the abdomen, three cases had mild pain and one case became restless and got nausea and vomiting.

In the normal series, three cases complained of severe pain in abdomen and one had more bleeding, 2 and 3 hours after delivery of anterior shoulder. One case had mild pain in abdomen and one case got severe bleeding, needing morphia and ergometrine. One of the subjects had hydramnios.

Discussion

As revealed by statistical analysis of the data, synthetic oxytocin (syntocinon) significantly decreased the duration of the third stage of labour and also the third stage bleeding. Since in none of the cases the placenta was trapped it appears that the drug has a definite place in the armamentarium of an obstetrician, since even in normal labour it decreases the duration of the third stage and also there is less third stage bleeding. Davis and Kuhlman (1958) also found that syntocinon decreases the third stage bleeding and duration of the third stage without causing trapping of the placenta. In fact, they have emphasised that 'the fear of trapping the placenta by this method is more a delusion than a reality'. Luby et al (1959) also observed diminution of the third stage with syntocinon. Caldeyro-Borcia (1958) has described that syntocinon in physiological doses increases the intensity and fre-

quency of contractions of uterine muscles without significantly raising the tone. They have remarked that oxytocin infusion is the most accurate, safe, efficient and easy way to increase uterine contractility for the induction and/or enhancement of labour. If, however, the dose exceeds physiological limits, then it produces uterine hypertonus and uterine tachysystolia.

Luby et al (1959) employed syntocinon in labour by giving 5 units intravenously and 5 units intramuscularly with delivery of the head. Devis and Kuhlman (1958) used 10 units of syntocinon intravenously just prior to delivery of the head in one series and after delivery of the baby in another series. Konzelt (1960) mentions that very slow intravenous infusions of oxytocin do not affect the blood pressure significantly but a rapid intravenous injection of even 0.2 units of syntocinon produces a transient but marked fall of blood pressure in human subjects. With higher doses (0.4-2 units) fall of blood pressure becomes more marked, attended with tachycardia. Mayes and Shearman (1956) report flattening of T wave of the electrocardiogram with intravenous injections* of 3-5 units of syntocinon. Kitchin et al (1959) found vasodilatation in hand and fore-arm of human subjects attended with a short lived fall of blood pressure and tachycardia with doses of the order of 200 m units for a single intravenous injection and 400 m units/mt. for an infusion of synthetic oxytocin. Hibbard and Andrews (1960) in their studies with intravenous infusion of syntocinon have remarked that "when syntocinon was adminis-

tered by intravenous infusion during labour, a physician or experienced nurse was present at all times to observe the strength and frequency of uterine contractions. When the observer was a nurse, the physician remained in the hospital and close at hand. This is essential because both the optimal and safe rates of administration are variable and depend entirely on the initial and continued response of the individual patient". As already cited earlier, Mayes and Shearman (1956) encountered 'oxytocin shock' and myocardial depression with intravenous administration of synthetic oxytocin.

From the fore-going account it is clear that intravenous injection or infusion of oxytocin is not free from danger and as such cannot be recommended as a routine procedure. It can only be used with caution in a hospital where proper facilities for continuous observation of the patient exist.

Sem (1958) remarks that since oxytocin is very rapidly destroyed by serum oxytocinase it is necessary to aim at maintaining an optimal uniform blood level of the drug while giving it intravenously. Perhaps, during pregnancy, some mechanism develops (Mendez-Baner and Caldeyro-Borcia, 1957) which protects oxytocin from this very rapid destruction. Even then plasma removed at term produces 50% inactivation of oxytocin within 7 minutes.

It, therefore, appears that in the intravenous administration of oxytocin one is not only running the risks enumerated above but is also not sure of maintaining uniform levels of the drug in the blood reaching the uterus due to the factor of inactiva-

tion by serum oxytocinase.

In the present study synthetic oxytocin (syntocinon) was, therefore, given as a single intramuscular injection (10 units) after birth of the anterior shoulder since the aim was to study its beneficial effects, if any, on the third stage duration and the third stage bleeding.

Analysis of the data regarding the effects of syntocinon on systolic blood pressure shows that the incidence of increase in blood pressure up to 20 minutes is greater in syntocinon series than in the normal series. The incidence of fall in systolic blood pressure was less with syntocinon than without it. Drill (1958) mentions that in the human subject oxytocin produces vasodilatation most commonly. It, therefore, appears that the slightly greater incidence of rise of systolic pressure in the first 20 minutes is perhaps due to the stronger contractions of the uterine muscle increasing the venous return to the heart and thus raising cardiac output and blood pressure, the later effect predominating over the vasodepressor tendency due to vasodilatation. In the syntocinon series there was only one case having initial systolic blood pressure of 160 mm. Hg. In her the maximum rise in systolic pressure was of the order of only 10 mm. Hg. at 10 minute period and then it started falling till it reached a level of 20 mm. Hg. below the initial blood pressure at the end of 3 hours. The pressor effect on the diastolic blood pressure is even less marked in all cases.

It, therefore, appears that synthetic oxytocin (syntocinon) does not raise the blood pressure signi-

ificantly when given by intramuscular injection and can be used even in cases having initial systolic pressure of 160 mm. of mercury. It also appears that if administered intramuscularly, it does not produce alarming fall of blood pressure or 'oxytocin shock'.

The effects of syntocinon on diastolic blood pressure are even less marked than those on systolic pressure.

Summary

Synthetic oxytocin (Syntocinon) has been used by intramuscular injection of 10 units on birth of the anterior shoulder in 50 normal child-births, alternated with 50 normal child-births in which no oxytocin or similar drug was used. Syntocinon has been found to significantly decrease the duration of the third stage of labour and the third stage bleeding. Use of the drug by intramuscular injection has not produced either alarming rise or fall of blood pressure. In no case was the placenta trapped. The incidence of severe pain in abdomen was practically similar in the two series. No anaesthesia was employed in any case.

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