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CONCENTRATED SERUM IN TREATMENT OF TRAUMATIC AND HISTAMINE SHOCK IN EXPERIMENTAL ANIMALS

BY

C. H. BEST, M.D.Toronto, D.Sc.Lond., F.R.S.

Professor of Physiology, University of Toronto

AND

D. Y. SOLANDT, M.D.Toronto, Ph.D.Lond.

Associate Professor of Physiology, University of Toronto

(From the Departments of Physiology and Physiological Hygiene, University of Toronto)

The work of Cannon and Bayliss (1919) during the last war provided an experimental basis for the development of methods for treating wound shock. They demonstrated that effective treatment must restore vascular tone and blood volume.

It is generally agreed that one of the first pathological changes in severe traumatic shock is the fall in the volume of circulating blood. This results in a deficient return of blood to the heart and thus in the low blood pressure characteristic of the condition. The loss of circulating blood may be due to any or all of three causes: it may be the result of frank haemorrhage from injured vessels, of fluid exudation from atonic capillaries, or of stagnation in a dilated capillary bed. Some believe that exudation and stagnation are limited to the wound site (Blalock, Beard, and Johnson, 1931). Others maintain that from the injured tissue is set free a toxic substance which affects capillaries throughout the body, producing these effects remote from the site of injury (Cannon and Bayliss, 1919; Moon, 1936). It is possible that the cause and effect of capillary atony constitute a vicious circle: the embarrassment of the circulation initiated by the atony may result in an ischaemia of arteriolar and capillary walls, thus maintaining the atony after the original causative agent has been removed.

Methods of treating shock must aim at halting these processes and correcting their results. Pituitrin and adrenaline were used extensively and fairly effectively during the last war for the temporary correction of vascular atony. Restoration of blood volume was attempted by the intravenous administration of various aqueous solutions with suitable osmotic characteristics. The most effective of these was gum acacia solution, the administration of which we now know may be attended by grave dangers (Studdiford, 1937; Hall, 1938). Recently Bond and Wright (1938) have used for this purpose blood serum concentrated by the "lyophile" process. Levinson and co-workers (1940) have shown the value of unconcentrated blood serum in the treatment of post-haemorrhagic shock in experimental animals. It is possible that the presence of abnormal amounts of fluid in certain tissues during shock is detrimental, apart from the loss in blood volume which is represented. If this is so treatment should aim at the return of this fluid to the blood stream. This is readily accomplished by the intravenous administration of a hypertonic fluid.

The present work was undertaken with a view to evaluating certain methods of treating shock in experimental animals. We felt that any procedure useful in severe shock should be initiated by the administration of a vasoconstrictor, temporarily to correct vascular atony so that solutions introduced into the blood stream are not lost immediately into tissue spaces. This having been done the blood volume should be increased by an osmotically adequate solution of biologically acceptable constituents. It was hoped that this procedure would break the vicious circle which may be responsible for vascular atony and that adequate vascular tone thus initiated would be maintained after the effects of the vasoconstrictor had worn off. In selecting a solution for the restoration of blood volume it seemed logical to choose one which would reduce tissue fluids. Concentrated blood serum fills all these requirements and has the additional advantage that, unlike whole blood, it may be kept indefinitely without deterioration.

Methods

Dogs under deep nembutal anaesthesia were used in all experiments. Blood-pressure records were taken with a mercury manometer connected to a cannula in a carotid artery. Cell-volume estimations were made with a haematocrit. Blood volume was measured by the dye method, using Evans blue dye and a photo-electric colorimeter (Gregersen, 1938; Kennedy and Millikan, 1938). Serum-protein determinations were made by estimating protein nitrogen in trichloroacetic acid precipitates by the micro-Kjeldahl technique. The initial experiments were performed on animals in histamine shock. Histamine was given in a first dose of approximately 0.5 mg. per kg. of body weight, and this was repeated at decreasing intervals until the blood pressure remained below 50 mm. Hg (Dale and Laidlaw, 1918). Traumatic shock was obtained either with or without extensive haemorrhage. If the former was desired a large animal (15 to 20 kg.) was chosen and, under deep anaesthesia, each thigh was given about ten blows with a heavy steel hammer. In such an animal shock developed in less than one hour and was probably chiefly due to the haemorrhage. If shock without extensive haemorrhage was required a small animal (5 to 8 kg.) was chosen, and the thigh muscles were given a total of 1,000 to 2,000 light blows with a rubber mallet. Shock, as indicated

by a blood pressure of below 50 mm. Hg. developed in three to five hours after the trauma was inflicted. All animals were kept deeply anaesthetized during the entire experiment and were killed at the termination.

The concentrated serum used was prepared by evaporating dog-blood serum to one-third its normal volume by Thalheimer's (1939) technique. In this method the serum is placed in closed cellophane sacs, and these are exposed to dried air, which removes water from the surface of the sac. In every case the sera from a number of dogs were pooled. Serum to be used for treating a dog was tested on that animal before the procedure for inducing shock was started. If any untoward reaction occurred serum from another pool was used. Typed human serum prepared by this method has thus far produced no harmful reaction in patients in the limited experience of Dr. Thalheimer (personal communication) or of our clinical colleagues.

Results and Discussion

Low blood pressure was taken as the essential index of shock. Since survival experiments were not feasible the effectiveness of treatment was judged chiefly by the extent and duration of the rise in blood pressure which it produced. Blood-volume, cell-volume, and blood-protein determinations were used to give additional information concerning the severity of shock and the efficacy of treatment.

The results of the treatment of histamine shock are given in Table I. A stable blood pressure at a shock level was seldom seen in these experiments: most of the animals treated had systolic pressures below 50 mm. Hg. As indicated, such animals obtained the greatest benefit from the administration of a vasoconstrictor substance followed by a liberal quantity of concentrated serum. A blood-pressure tracing taken during this type of treatment is shown in Fig. 1. Trauma with haemorrhage produced a sudden fall in blood pressure which occurred at the time the injury was produced. Following this the blood pressure fell slowly, and eventually became stabilized at a low level. The results obtained in the treatment of such shock are set forth in Table II. The

best treatment was found to be the same as for histamine shock, and a blood-pressure tracing made during such a procedure is shown in Fig. 2. Trauma without extensive haemorrhage resulted in only a slight and gradual fall in blood pressure at the time the injury was produced. This was followed by a rise and then a slow steady fall in blood pressure. As a rule the blood

FIG. 1.—Treatment of histamine shock. Blood-pressure tracings (18-lb. dog).

FIG. 2.—Treatment of traumatic shock with haemorrhage. Blood-pressure tracings (14-lb. dog).

FIG. 3.—Treatment of traumatic shock without extensive haemorrhage. Blood-pressure tracings (10-lb. dog).

pressure dropped to below 50 mm. Hg in from two to four hours after the trauma was produced. Table III shows the results of the treatment of such shock. Again the administration of a vasoconstrictor substance followed by concentrated serum seemed the best form of treatment if the blood pressure was under 50 mm. Hg. Fig. 3 shows a blood-pressure tracing taken during such treatment. When the blood pressure was above a level of approximately 50 mm. Hg the concentrated serum without the vasoconstrictor was effective.

Treatment of Shock in Dogs

	Dog		Blood Pressure (Systolic)			Treatment†		
	No.	Wt.	Normal	Shock Level	Following Treat-ment*	Adrena-line (1:1,000)	Pituitrin	Concentrated (3x) Serum
Table I: Histamine Shock		lb.	mm. Hg	mm. Hg	mm. Hg	c.cm.	c.cm.	c.cm.
	1	16	150	40 (falling)	88	—	—	20
	2	22	153	25 "	25	—	—	40
	3	18	102	40 (steady)	90	—	0.50	40
	4	15	210	55 (falling)	100	—	0.25	25
	5	22	153	25 "	78	0.10	—	50
Table II: Traumatic Shock with Haemorrhage	6	12	165	30 "	50	0.10	—	50
	7	19	190	68 (steady)	110	—	—	40
	8	19	190	60 (falling)	80	—	—	40
	9	20	135	22 "	70	—	0.25	20
	10	14	140	30 "	80	—	0.25	40
	11	16	160	20 "	50	0.10	—	20
Table III: Traumatic Shock	12	47	130	35 "	90	0.10	—	50
	13	31	164	20 "	70	0.10	—	60
	14	20	180	56 (falling)	75	—	—	25
	15	16	160	50 "	100	—	—	40
	16	12	180	30 "	30	—	—	20
	17	12	160	50 "	100	—	0.25	20
	18	21	140	60 "	90	—	0.25	40
	19	10	180	35 "	85	—	0.25	50
	20	13	160	55 "	90	—	0.25	20
	21	33	190	55 "	90	—	0.25	40
	22	11	180	35 "	70	—	0.25	20
	23	12	180	18 "	85	0.10	—	60
	24	10	160	25 "	70	0.10	—	40
	25	15	180	48 "	70	0.10	—	40

* This pressure was maintained for the period of observation (never less than 1 hour) following treatment.

† Vasoconstrictor followed by concentrated serum.

Treatment with vasoconstrictor substances alone was tried in all three types of shock. Our results confirm those of previous investigators. A single dose of adrenaline produced a sudden rise in blood pressure with almost immediate return to the old level. By the continuous administration of adrenaline at a fixed rate it was possible to maintain the blood pressure at a normal level for many hours, but when the injection was stopped the blood pressure returned to the shock level. It is of interest that there seemed to be little adaptation to adrenaline administered continuously over a number of hours. On the other hand, pituitrin administered continuously elicited rapid adaptation, and to be effective the dose had to be progressively increased. As is well known, pituitrin given in a single dose produces much slower but more prolonged rise in blood pressure than does adrenaline. Pituitrin alone, however, like adrenaline, does not have a prolonged beneficial effect on the blood pressure of shocked dogs.

Our experimental results indicate that, unless the blood pressure is very low, pituitrin rather than adrenaline is the vasoconstrictor to use preceding the administration of concentrated serum. Usually the serum was given when the pressure was rising under the influence of the vasoconstrictor. In this way it was thought that leakage of the serum through the walls of dilated blood vessels might be minimized. The fact that this procedure in many cases yielded a relatively permanent rise in blood pressure, such as was never seen under comparable conditions after the administration of either the concentrated serum or the vasoconstrictor alone, lends support to this view.

In a few experiments in which the blood pressure had fallen to very low levels pituitrin produced no rise. In several of these the subsequent administration of adrenaline followed by concentrated serum raised the systolic blood pressure from under 20 mm. Hg to over 70 mm. Hg, where it remained for several hours. Fig. 4 shows the blood-pressure record of such an experiment.

FIG. 4.—Treatment of very severe traumatic shock without haemorrhage. Blood-pressure tracings (12-lb. dog).

Many other workers (Bayliss, 1918; Cannon, 1923; Moon, 1938; Scudder, 1940) have shown that the effect of isotonic or hypertonic dextrose or salt solutions on low blood pressure is quite transient. In our experiments the immediate effect of the osmotically equivalent 20 per cent. dextrose, 3 per cent. sodium chloride solution, or three-times-concentrated blood serum seemed to be about the same. The effect of the dextrose is much more prolonged than that of the salt solution, but even in our short-term experiments dextrose was in some cases demonstrably inferior to concentrated blood serum. Dextrose may have a vasoconstrictor action, as in a few cases it alone was initially as effective as concentrated serum preceded by pituitrin. It is also possible that the dextrose provides a readily available source of energy to ischaemic muscle in heart and blood-vessel walls, and in the past it has often been added to solutions for intravenous administration with this possibility in mind.

In the case of dextrose, salt solution, or blood serum the hypertonic (concentrated) form was found to have a much more pronounced initial effect on the low blood pressure of traumatic shock than the same volume of the isotonic form. This indicates that the concentrated material effectively removed fluid from the tissues into the blood stream. As previously mentioned, this may be beneficial quite apart from the increase in blood volume thus produced. Such removal can only take place when the capillary walls retain their normal function as semi-permeable membranes. This provides a further reason for the administration of pituitrin before the concentrated serum is given.

Haematocrit determinations indicate that in all three types of shock there is a concentration with respect to red blood corpuscles. Blood-protein determinations, however, indicate an actual blood dilution. Both changes are, in part at least, reversed by effective treatment as outlined. Blood-volume determinations are of doubtful validity in the presence of shock (Neuwelt, 1939), but usually indicate that the quantity of circulating blood is decreased in shock and that this value is returned towards normal by adequate treatment. These findings merely substantiate those of earlier workers (Mann, 1915; Bazett, 1918; Keith, 1919), and therefore are not given in detail.

Conclusions

In the above experiments some seventy animals were studied. Ten of these were so severely shocked that no form of treatment was effective. In the remaining cases the treatment resulted in varying degrees of improvement, and the tables and figures give representative results from this group. The results of experiments of the type described are very difficult to evaluate. No two animals react in exactly the same manner to either the shock-producing procedure or the treatment. A statistical evaluation of the methods we have used for treating shock is thus impossible. Our studies have, however, enabled us to draw certain definite conclusions concerning the treatment of shock in experimental animals.

In so far as treatment is concerned, shocked animals respond in the main similarly, whether the condition is initiated by histamine administration, trauma with extensive haemorrhage, or trauma with little or no haemorrhage. When the blood pressure is between 25 and 50 mm. Hg the best form of treatment which we have thus far tested is the intravenous administration of a single dose of pituitrin followed by an adequate quantity of concentrated blood serum. If some time later the blood pressure again starts to fall this treatment may be repeated with benefit. If the shock level of blood pressure is very low adrenaline may prove more effective than pituitrin. If the blood pressure is relatively high—above 50 or 60 mm. Hg—the concentrated serum alone may be quite effective.

Our experiments indicate that, in traumatic shock at least, the injection of a hypertonic fluid is more beneficial than an isotonic one of the same constituents. We believe that the results of these experiments on animals should encourage a trial of pituitrin and concentrated human blood serum on patients suffering from severe traumatic shock.

Summary

Shock in experimental animals was produced by histamine administration, by trauma with extensive haemorrhage, and by trauma with little or no haemorrhage. These three types of shock were successfully treated by the intravenous adminis-

tration of pituitrin and concentrated blood serum. The possible clinical application of these results is pointed out.

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SUCCESSFUL CHEMOTHERAPY FOR HAEMOLYTIC STREPTOCOCCAL MENINGITIS AND PNEUMO- COCCAL MENINGITIS IN THE SAME PATIENT

BY

W. OGILVY REID, M.A., B.Sc., M.B., Ch.B.,
F.R.C.S.Ed.

Late Acting Medical Superintendent, the Downs Hospital
(L.C.C.), Sutton, Surrey

AND

JOHN F. LIPSCOMB, M.B., B.S., F.R.C.S.

Acting Deputy Medical Superintendent at the Hospital

There are many published reports of successful treatment of haemolytic streptococcal meningitis with sulphanilamide and other sulphonamides. So striking are the results that one would be justified, when recording the history of the treatment of this disease, in drawing a line between what may be called the pre-sulphonamide and the sulphonamide eras. In the former period the outlook was gloomy in the extreme. Gray (1935), in his classical analysis of the sixty-six cases of recovery from streptococcal meningitis recorded in the whole literature of the subject between 1901 and 1935, gave the mortality rate as 97 per cent. In pneumococcal meningitis the story was even more depressing, the mortality being little short of 100 per cent. With the advent of chemotherapy by sulphonamides this form of treatment was applied to streptococcal meningitis with most dramatic results. Figures such as those published by Appelbaum (1939) have become quite common. He had thirty-five cases with twenty-eight recoveries and seven deaths—the majority of the latter having other complications which might themselves have proved fatal.

Successful chemotherapy in pneumococcal meningitis was uncommon until the introduction of sulphapyridine (M & B 693), although recoveries have been reported by Caldwell and Byrne (1937), Latta (1938), Landon (1938), Young (1938), and others. Hodes, Gimbel, and Burnett (1939) report seventeen cases of pneumococcal meningitis treated with sulphapyridine and its sodium salt, eight

recovering. They contrast these results with those obtained at the Sydenham Hospital, Baltimore, before the introduction of the drug: between 1930 and 1936 twenty-seven cases were admitted and all were fatal; from December, 1936, to October, 1938, seventeen patients were treated with sulphanilamide, with one recovery. These authors state that previous to the publication of their paper eight recoveries had been recorded out of fourteen cases of pneumococcal meningitis treated by sulphapyridine alone. If these are added to their own cases we have, with the case described below, thirty-two cases of pneumococcal meningitis treated by sulphapyridine alone, with seventeen recoveries, a rate of 53 per cent. It would appear, therefore, that the introduction of sulphapyridine has so far halved the mortality rate.

A search of the literature has, however, failed to reveal any record of a patient having recovered from two distinct attacks of coccal meningitis bacteriologically different in origin, and the uniqueness of the following case in this respect would appear to justify its publication.

Case History

The patient was a girl aged 17 whose previous medical history was uneventful, except that she had had a mild attack of acute otitis media in childhood which had completely resolved.

FIRST ATTACK (STREPTOCOCCAL MENINGITIS)

On August 24, 1937, the patient was admitted to hospital with acute otitis media following tonsillitis, and six days later a Schwartze mastoidectomy was performed. Progress was satisfactory until September 8, nine days after the operation, when the temperature rose and there was headache and neck stiffness. Her condition rapidly deteriorated; within a few hours unconsciousness supervened with all the signs of a virulent meningitis. Cerebrospinal fluid withdrawn under pressure was turbid, the cell count being 11,040 per c.mm., and haemolytic streptococci were grown on culture. Chemotherapy was started on the 9th, 5 c.cm. of prontosil soluble being injected intramuscularly. On the following day two further injections were given. Mr. Terence Cawthorne converted the Schwartze to a radical operation, and released cerebrospinal fluid under extreme pressure by incision of the dura of the posterior fossa (Neumann's procedure). The next day tablets of sulphanilamide were given, being continued for eight days (see "Dosage").

The second cerebrospinal fluid specimen, withdrawn on September 12, was sterile, and the patient had regained consciousness, although still restless and averse to intervention. By the 16th her condition had improved so considerably that sulphanilamide was discontinued—a total of 27 grammes having been given. Excellent progress was maintained, the cerebrospinal fluid on October 18 being clear and containing only 30 cells. Suddenly, on October 20, severe headache, neck stiffness, photophobia, etc., recurred, the temperature rising more gradually to 102.2°. Drs. Sheldon and Denny Brown and Mr. Cawthorne all confirmed recrudescence of the meningitis, although the cerebrospinal fluid under increased pressure was sterile on culture. Sulphanilamide was again administered, and by October 25, after a further total dosage of 10.5 grammes, all signs of meningitis had once more disappeared. From that date convalescence was uninterrupted, and the girl was eventually discharged on December 17 cured—the affected ear being completely healed and dry.

In due course the patient was able to resume her duties as a nurse, and during the seventeen months which elapsed before her second illness she enjoyed very good health and experienced no sequelae. Recurrent headaches of which she complained were eliminated by the provision of glasses, and she had been free from them for some six months before the second attack.

SECOND ATTACK (PNEUMOCOCCAL MENINGITIS)

On the morning of May 13, 1939, the patient was first seen by one of us, having been complaining of vomiting, vertigo,