ATTEMPTS TO PROLONG AND INTENSIFY SPINAL ANESTHESIA BY THE ADDITION OF EPHEDRINE, NEOSYNEPHRIN OR EPINEPHRINE TO A PONTOCAINE-GLUCOSE SOLUTION *

WARREN F. SERGENT, M.D.,† AND ROBERT D. DRIPPS, M.D.
Philadelphia, Pa.

Received for publication April 9, 1948

VARIOUS substances have been added to spinal anesthetic agents in an attempt to prolong their action. Starch, gliadin and human plasma have all been used for this purpose. More popular, however, are the drugs which raise blood pressure—ephedrine, neosynephrin, methedrine and epinephrine having been studied. It was assumed that these drugs might produce the desired result through local vasoconstriction and prevention of vascular absorption of the anesthetic from the subarachnoid space. It has also been suggested that the pressor drugs themselves may, through a direct action on nerve roots, produce partial degrees of block of conduction in these roots (1, 2). Another possibility is that the pressor drugs might exert an antagonistic action against those enzymes which destroy local anesthetic drugs. There is no evidence at the moment for this postulate.

A few studies on animals and many clinical reports have appeared recently, indicating (a) that the duration of anesthesia is prolonged to varying degrees by different pressor drugs; (b) that the effective dose of a spinal anesthetic agent can be reduced by such a combination, and (c) that ephedrine, at least, may be able to produce nerve block in its own right (2–6).

We have attempted to assess the value of such a combination by analyzing statistically any change in the increased duration of sensory and motor block which resulted from the addition of a pressor drug. Ephedrine, neosynephrin and epinephrine have been studied.

METHOD

A standard dose of pontocaine hydrochloride was administered to each of 539 patients. Ten milligrams of a 1 per cent solution of the drug, i.e., 1 cc., was used. A standard total volume of 3 cc. was injected in each instance. The remainder of the total volume was made up as noted below.

* From the Division of Anesthesiology, Hospital of the University of Pennsylvania, and the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine, Philadelphia, Pa.

† Dr. Sergent is now at the St. Joseph's Hospital, Lexington, Ky.

As a control group, 105 patients received the above drugs to which was added 1 cc. of spinal fluid withdrawn at the time of the lumbar puncture. Two hundred and eighteen patients received 50 mg. of ephedrine sulfate (1 cc. of a 5 per cent solution) added to the pontocaine-glucose mixture. One hundred and six patients received 1 mg. (0.5 cc. of a 0.2 per cent solution) of neosynephrin hydrochloride and 110 were given 0.5 mg. (0.5 cc. of a 0.1 per cent solution) of epinephrine. In the latter two groups 0.5 cc. of spinal fluid was added to bring the total volume to 3 cc. (table 1).

TABLE 1

No. of Cases	Pontocaine 1%, mg.	Glucose 10%, cc.	Pressor Drug	Spinal Fluid, cc.	Total Volume, cc.
105	10	1	None	1	3
218	10	1	Ephedrine (50 mg.)	None	3
106	10	1	Neosynephrin (1 mg.)	0.5	3
110	10	1	Epinephrine (0.5 mg.)	0.5	3

Lumbar puncture was performed with a 20-gauge stileted needle, introduced into the third or fourth lumbar interspace. A pressor drug was usually administered intramuscularly prior to the lumbar puncture. The amount and type of this substance varied throughout the series.

TABLE 2

NUMBER OF CASES

	Control	Ephedrine	Neosynephrin	Epinephrine
1. *Age, years*				
0–19	3	18	3	5
20–29	13	27	12	16
30–39	15	44	18	14
40–49	29	54	19	23
50–59	23	47	26	37
60–69	15	19	24	9
70–79	5	7	4	5
80–89	2	2	0	1
2. *Sex*				
Male	60	117	48	50
Female	45	101	58	60
3. *Region of Operation*				
Upper Abdomen	23	61	24	23
Lower Abdomen	25	45	28	42
Inguinal	26	54	26	14
Below Inguinal	31	58	28	31

After injection of the anesthetic mixture the sensory level to pin prick was recorded at five to fifteen minute intervals during the operation and at thirty minute intervals after the operation until the level had receded to the twelfth thoracic or first lumbar segment. The dermatome classification of Foerster was used.

During the postoperative period patients were urged to move any portion of their lower extremities and the first voluntary movement was recorded as the end point of motor paralysis This might have been motion of a toe, or motion of the whole extremity.

Patients in the series were subjected to a variety of surgical procedures below the diaphragm. They ranged in age from 13 to 88 years; in weight from 97 to 270 pounds, and in height from 60 to 74 inches (table 2).

RESULTS

A. Duration of Motor Paralysis.—Motor paralysis of the lower extremity was considered as being present from the time of injection of the anesthetic agent until the first voluntary movement of any part of the lower extremity. Table 3 indicates the values found for the control series and for the groups given various vasoconstrictor drugs.

It is apparent that the addition of 50 mg. of ephedrine sulfate to the pontocaine-glucose mixture did not change the duration of motor block as we have defined it except in the perineal and lower extremity group. Neosynephrin and epinephrine in the dosages used prolong motor paralysis in all groups. The increased duration of block following these drugs was statistically significant. There was no essential difference between the two drugs from the standpoint of their ability to increase the time of motor block.

B. Duration of Sensory Anesthesia.—Sensory anesthesia was measured from the time of injection of the anesthetic mixture until the sensory level to pin prick had receded to the twelfth thoracic dermatome in all operations except those below the inguinal area; these were measured to the first lumbar. Table 4 lists the duration of anesthesia for the control and vasoconstrictor groups.

Again it is evident that ephedrine did not increase the duration of sensory anesthesia produced by the dose of pontocaine used in this series. Neosynephrin and epinephrine did increase the length of sensory block significantly according to statistical analysis. The difference in action of the two drugs was not significant.

C. Rate of Decline of the Sensory Level.—In an attempt to analyze the minute to minute effect of the addition of pressor drugs, graphs of those cases in which the sensory level of anesthesia reached or exceeded the fifth thoracic dermatome were constructed. The actual sensory level at fifteen to thirty minute intervals was charted for each patient (fig. 1).

TABLE 3

DURATION OF MOTOR BLOCK FROM TIME OF INJECTION UNTIL FIRST MOVEMENT OF LOWER EXTREMITY

Region		Control		Ephedrine			Neosynephrin			Epinephrine		
	Duration	Minutes	Cases	Minutes	Cases	Per Cent Increase	Minutes	Cases	Per Cent Increase	Minutes	Cases	Per Cent Increase
Upper Abdomen	Average	175	22	195	53	11	232.5	20	32**	259	20	48**
	Median	170		185			230			255		
	Range	105–270		115–330			150–315			195–345		
Lower Abdomen	Average	195	22	198	42	—	276	20	41**	276	36	41**
	Median	192.5		197.5			265			275		
	Range	95–270		130–315			180–410			140–390		
Inguinal	Average	180	25	205	46	13	255	23	41**	254	11	41**
	Median	175		205			245			255		
	Range	60–295		100–350			155–495			190–340		
Perineal and Lower Ext.	Average	149	27	196.5	48	31**	245	22	64**	248	24	66**
	Median	150		190			250			252.5		
	Range	65–260		75–315			85–400			135–350		
Total Average		173	96	198	189	14	252	85	45**	262	91	51**

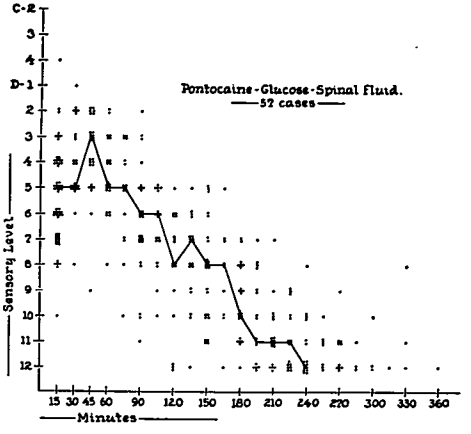
** Highly significant statistically (Fishers' t).

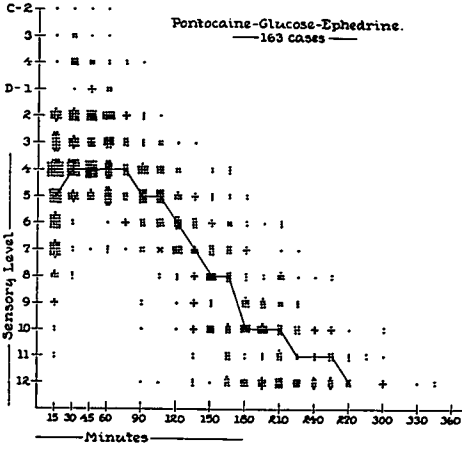
TABLE 4

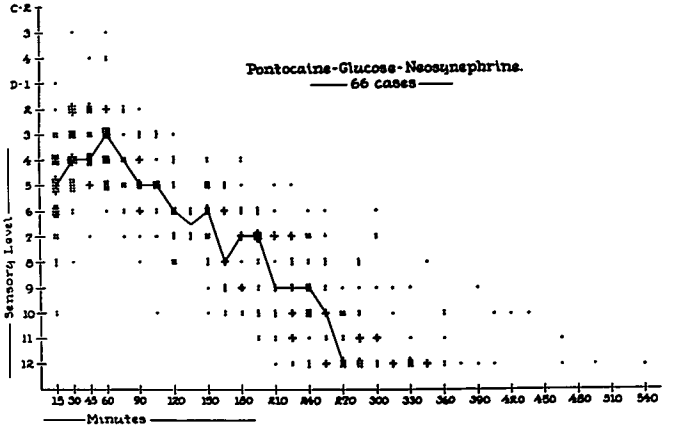
DURATION OF SENSORY BLOCK FROM TIME OF INJECTION UNTIL SENSORY LEVEL DESCENDED TO D_{12} OR L_1*

Region		Control		Ephedrine			Neosynephrin			Epinephrine		
	Duration	Minutes	Cases	Minutes	Cases	Per Cent Increase	Minutes	Cases	Per Cent Increase	Minutes	Cases	Per Cent Increase
Upper Abdomen	Average	244	22	238	40	—	294	18	20**	272	19	11
	Median	240		240			290			270		
	Range	130–160		150–315			225–340			195–330		
Lower Abdomen	Average	217	22	214.5	32	—	303	18	39**	277	37	27*
	Median	220		210			295			275		
	Range	120–300		135–315			200–395			170–390		
Inguinal	Average	236	21	223	38	—	294	19	24**	268	12	13*
	Median	230		217			285			267		
	Range	120–320		100–350			185–540			220–340		
Perineal and Extremity	Average	180	25	202	43	12	259	20	43**	265	25	47**
	Median	180		195			260			280		
	Range	65–275		105–340			165–445			150–380		

* Significant statistically.
** Highly significant statistically







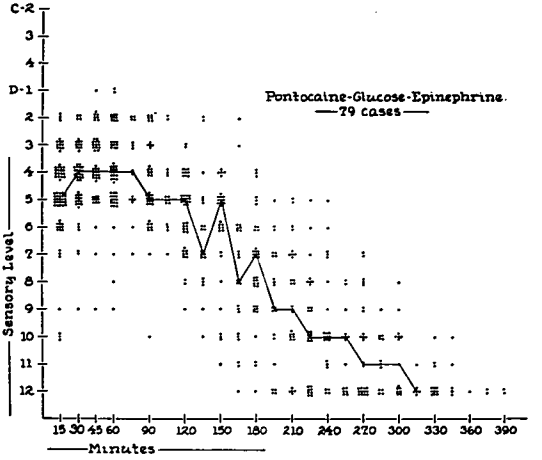


FIG. 1. Maintenance and rate of decline of the sensory level of spinal anesthesia as affected by the addition of a pressor drug to the anesthetic agent.—Only those cases in which the sensory level reached or exceeded the fifth thoracic dermatome are included.

Much of the information derived from these charts is similar to that described in section B. Certain additional facts are suggested, however. Patients receiving the ephedrine-pontocaine-glucose mixture responded with a higher level of anesthesia than did patients in the other groups. This was associated with a greater tendency for the ephedrine combination to "crawl" in a cephalad direction. It is uncertain whether these observations indicate a delay in fixation of the anesthetic agent, a greater tendency to rise because of the increased specific gravity of the mixture or a wider spread of anesthetic effect owing to a specific action of ephedrine itself.

The data suggest that the anesthesia produced by the addition of epinephrine tended to remain longer at the higher levels before beginning to recede. This interpretation of a more intense action is supported by figures listed in table 5.

D. Behavior during Operation.—The incidence of certain subjective complaints and objective findings is given in table 5.

TABLE 5

INCIDENCE OF REACTIONS DURING OPERATION

	Control	Ephedrine, *per cent*	Neosynephrin, *per cent*	Epinephrine, *per cent*
Emesis	6	8	8	10
Nausea and retching	27	32	30	28
Pain	17	8	22	7
Traction discomfort	26	16	20	15
Decrease in systolic blood pressure of 25 per cent or more from control systolic level	26	21	43	40

Nausea, retching and vomiting occur frequently during spinal anesthesia. A variety of causes may be listed for this reaction. One of these is the absorption of the local anesthetic agent into the blood stream with subsequent stimulation of a vomiting center in the central nervous system. If a pressor drug delayed vascular absorption of the anesthetic drug from the subarachnoid space it is possible that the incidence of nausea and vomiting might be reduced. The data in table 5 do not support such a contention.

The data in table 5 are of interest as one attempts to evaluate a possible change in the *intensity* of anesthesia produced by the addition of a pressor drug. The more complete the block of nerve roots the lower should be the incidence of pain experienced by the patient during operation. These data indicate that although the increased duration of block is about equal with neosynephrin and epinephrine, there is a more "solid" type of anesthesia produced by the addition of the latter drug. Ephedrine likewise appears to increase the intensity of the anesthesia if one can so interpret the figures for pain and traction discom-

fort listed in the table. Confirming the observations of others (3, 4) no evidence of any systemic action of the sympathomimetic drugs was found. The incidence of hypotension during anesthesia was, as a matter of fact, greater in the groups receiving neosynephrin and epinephrine.

E. Postoperative Complications.—All patients in the series were carefully observed during their stay in the hospital following operation. The incidence of the more common postoperative sequelae is presented in table 6.

TABLE 6

INCIDENCE OF POSTOPERATIVE SEQUELAE

	Control	Ephedrine, *per cent*	Neosynephrin, *per cent*	Epinephrine, *per cent*
Nausea and emesis	27	21	12	20
Urinary retention	15	13	8	11
Atelectasis and bronchopneumonia	4	8	9	3
Postural headache	5	6	5	10

From these data there is no evidence that the addition of a pressor drug is followed by an increased incidence of untoward effects. There were no instances of the cauda equina syndrome, adhesive arachnoiditis, transverse myelitis or radiculitis in the series.

DISCUSSION

It should be emphasized that the pontocaine-glucose mixture without a pressor drug produced anesthesia which varied widely in duration from patient to patient. Sensory anesthesia ranged from 65 to 320 minutes, motor block from 65 to 295 minutes. Any one patient might therefore respond to pontocaine alone with a block of five hours or more. For this reason, before valid conclusions can be reached as to the ability of a particular pressor drug to increase the duration of anesthesia one must study large numbers of patients and subject the results to statistical analysis.

Some of the data presented in this paper are at variance with opinions expressed by other authors (4–6). No increased duration of action as the result of the addition of 50 mg. of ephedrine sulfate to a standard pontocaine-glucose combination was demonstrated. This does not deny the possibility that the duration of action of a shorter-acting anesthetic agent such as procaine might be increased by ephedrine. Our results suggest, however, that such an increase would probably be insufficient to prove of much clinical value.

Neosynephrin and epinephrine in the amount used did prolong both sensory and motor block, although not to the extent recorded by other observers (3, 5, 6). Whether greater prolongation would have re-

sulted from different amounts of these pressor drugs was not determined. The possibility of there being some "ideal" concentration is real and this concentration may have been far from that used in this study.

Entirely apart from the problem of prolongation of action is the question of an increased intensity of effect. If it can be shown that sympathomimetic drugs produce this result one can either reduce the dose of the anesthetic agent as suggested by some (4), or, with the usual doses of spinal anesthetic agents, can anticipate less discomfort on the part of the patient during surgical manipulation.

Possibilities of harm from the introduction of a vasoconstrictor drug into the subarachnoid space should be considered. Several theoretical objections can be raised. (a) Vasoconstriction might lead to anoxia of nerve tissue through local reduction of blood supply. Reversal of whatever mechanism is responsible for the production of nerve block might therefore be less likely. To date, there has been no evidence of increased neurologic sequelae following such practices. (b) A patient under spinal anesthesia might show extensive muscular block with respiratory inadequacy. In such instances the shorter the action of the anesthetic agent the more rapidly can normal conditions be restored. (c) Muscular activity is alleged to minimize venous thrombosis. Excessive prolongation of spinal anesthesia might, therefore, be followed by an increased incidence of such vascular disturbances. (d) Use of an increased number of ampules in preparation for a spinal anesthesia increases the chance of contamination. This objection, of course, could be corrected by marketing a single ampule.

Although there are no convincing data to confirm these theoretical objections it seems wise to proceed cautiously until more is learned of the nature of the action of pressor drugs in prolonging or intensifying spinal anesthesia. The gain may not be worth the price.

CONCLUSIONS

1. The efficacy of ephedrine, neosynephrin and epinephrine in prolonging and intensifying spinal anesthesia produced by pontocaine has been studied in a controlled series of 539 patients.

2. With the dosage used and under the conditions of the study, ephedrine proved ineffective except in possibly intensifying the action of pontocaine. Neosynephrin and epinephrine were about equally effective in prolonging both sensory and motor block. Epinephrine appeared to maintain a particular initial sensory level longer than neosynephrin. The prolongation of action associated with the use of pressor drugs was less than reported by other workers.

3. No neurologic sequelae were noted in this series.

4. Possibilities of harm from such a practice were discussed. It was suggested that the ultimate use of pressor drugs in the subarachnoid space may depend upon elucidation of the mechanism of action of these agents.

REFERENCES

1. Schultz, F. H.: Local Anesthetic Properties of Ephedrine Hydrochloride, Anesthesiology 1: 69–71 (July) 1940.
2. Ruben, J. E.; Kamsler, P. M., and Howell, W. L., Jr.: The Spinal Anesthetic Effects of Ephedrine Sulfate: A Preliminary Report, Science 107: 223–224 (Feb.) 1948.
3. Prickett, M. D.; Gross, E. G., and Cullen, S. C.: Spinal Analgesia with Solutions of Procaine and Epinephrine, Anesthesiology 6: 469–475 (Sept.) 1945.
4. Potter, J. K., and Whitacre, R. J.: Pontocaine-Dextrose-Ephedrine for Spinal Anesthesia, Anesthesiology 7: 499–504 (Sept.) 1946.
5. Romberger, F. T.: Spinal Anesthesia—Practical Facts and Common Fallacies—Clinical Research on Prolonged Spinal Anesthesia Using Vasoconstrictor Adjunctives, Anesth. & Analg. 22: 252–263 (Sept.-Oct.) 1943.
6. Shane, S. M., and Ruiz, E. T.: Use of Adrenalin to Prolong Spinal Anesthesia, Am. J. Surg. 74: 189–191 (Aug.) 1947.