AN EVALUATION OF HYALURONIDASE IN LOCAL AND NERVE BLOCK ANALGESIA: A REVIEW OF 519 CASES *

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Received for publication November 16, 1949

DURING the past four years we have been seeking drugs, methods, and technics to facilitate the use of regional analgesia (1, 2). In the early part of the present decade some research has been undertaken on the factors controlling spread and absorption of solutions injected into the body tissues (3, 4, 5, 6). More recently this has increased with experimental and clinical work on hyaluronidase (7, 8, 9, 10, 11, 12, 13, 14, 15, 16). Some authors have claimed that hyaluronidase increases the area of skin anesthesia in local infiltration by 40 per cent (14). If this were true we thought that hyaluronidase might be a useful adjuvant in nerve block analgesia. Duran-Reynals and Cosentino suggested employing hyaluronidase in local anesthetic procedures but did not record any experimental or clinical data (4, 17). Many surgeons and anesthesiologists avoid the use of this type of analgesia because they are unable to obtain satisfactory results in a high percentage of cases. If some factors which would cause spread of the anesthetic solution in the tissues were available this objection might be eliminated. With this in mind we decided to study 519 unselected cases employing hyaluronidase.

ESSENTIAL PHARMACOLOGY OF HYALURONIDASE

Hyaluronidase is now generally conceded to be the "spreading factor" of Duran-Reynals and McClean (4, 5). The enzymatic action of hyaluronidase, the mucolytic enzyme, hydrolyzes hyaluronic acid, a viscous polysaccharide found in the interstitial spaces of the tissue where it normally obstructs diffusion of invasive substances. When no spreading factor is present, the spread of injected materials is slow because of being limited by the hyaluronic acid in the tissues. Hyaluronidase, by neutralization of the hyaluronic acid, however, will cause rapid spreading if the interstitial pressure is adequate to furnish the necessary mechanical impulse. Such an impulse is normally initiated by

* 100 ampules of Hydase were supplied by Wyeth and 100 ampules of Diffusin were supplied by Ortho Pharmaceutical Corporation. Pontocaine Hydrochloride furnished through the courtesy of Winthrop-Stearns, Inc.

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injected solutions. The rate of diffusion is proportionate to the amount of enzyme, and the extent is proportionate to the volume of solution (8, 13).

Hechter found that the natural hyaluronic acid barrier was partly restored in twenty-four hours and completely restored in forty-eight (18).

TABLE 1

TYPES OF NERVE BLOCKS PERFORMED

Nerve Block and Local Infiltration	Pontocaine-Hyaluronidase*			Pontocaine (Control)*		
	No. of Therap., Diagnostic Blocks	No. of Surgical Blocks	No. of Patients	No. of Therap., Diagnostic Blocks	No. of Surgical Blocks	No. of Patients
1. Brachial		52	52	2	270	245
2. Breast (Brachial, Superficial cervical, Intercostal $T_1 - T_5$)		5	4		9	8
3. Cervical (deep and superficial)		61	61	4	67	71
4. Hernia		21	21		37	37
5. Infiltration	8	16	22		18	18
6. Intercostal (bilateral) and deep splanchnic		129	127	2	83	85
7. Intercostal (bilateral and unilateral)	61	3	34	141	8	87
8. Lumbar sympathetic	35		12	19		12
9. Mandibular		3	3	1	9	10
10. Maxillary		2	2	4	1	2
11. Maxillary—mandibular	2	3	5		4	4
12. Maxillary, mandibular and deep cervical		2	2		1	1
13. Median, radial, ulnar (at wrist or elbow)		3	3		19	19
14. Mental		5	5		5	5
15. Obturator	3		3	2		2
16. Paravertebral	6		5	22	9	28
17. Paravertebral (angina)	5		4	2		2
18. Sciatic and femoral	2	51	53	5	119	124
19. Splanchnic (deep)	3		3	5		4
20. Stellate	10		10	95		47
21. Suprascapular	5		3	2		2
22. Sciatic, femoral, obturator, and lateral femoral cutaneous		2	2		1	1
23. Transsacral (2, 3, or 4)	1		1			
	141	358	437	306	660	814

* With and without a vasoconstrictor drug.

Therapeutic doses of hyaluronidase are nontoxic and the ratio of toxicity to the therapeutic dose is 200,000 to 1 (19). Hyaluronidase has no effect on body temperature or the kidney, and in clinical use there has been no evidence of toxic or allergic reaction (8, 10, 11, 19). Hyaluronidase can penetrate a fibrin barrier only if injected into it; otherwise, the drug diffuses around it and follows the path of least resistance (13).

PROCEDURE

Four hundred ninety-nine infiltration and nerve block procedures were carried out with solutions of pontocaine hydrochloride, ranging in concentration from 0.1 per cent to 0.5 per cent (tables 1 and 2). The total amount of pontocaine employed in any one block ranged from 50 mg. to 250 mg. (table 2). The volume of solutions employed

TABLE 2

PERCENTAGE COMPARISONS

Pontocaine per cent	No. of Cases	Dosage Used				Reactions to Pontocaine-Hyaluronidase Solution	
		Maximum, cc.	Maximum, mg.	Average, cc.	Average, mg.	With Vasopressor	Without Vasopressor
0.1	120	250	250	150	150	0	0
0.15	128	110	165	85	125	5	0
0.20	13	100	200	60	125	0	0
0.25	208	100	250	50	125	8	1
0.3	19	40	120	40	100	0	0
0.4	7	30	120	30	120	0	0
0.5	4	40	200	10	50	0	0

ranged from 5 cc. of the concentrated solutions to 200 cc. of dilute solutions (table 2). The volumes and concentrations of the local anesthetic agents and the vasopressor drug for the control series and this series were essentially comparable for the same procedure, except for the addition of hyaluronidase. For example, a brachial block in the control series was executed with 50 cc. of 0.25 per cent pontocaine with or without a vasopressor, and a brachial block in this series was performed with 50 cc. of 0.25 per cent pontocaine plus hyaluronidase with

TABLE 3

PHYSICAL STATUS RECORD
American Society Anesthesiology Code

Age Group, years	1	2	3	4	5	6	7	Total
0–10	2				2			4
11–20	11	2	1		8			22
21–30	27	6	1		3			37
31–40	44	11		1	8			64
41–50	69	18	4	3	25			119
51–60	48	33	9	3	20			113
61–70	30	37	17	3	15	2		104
71–80	1	10	11	1	7			30
81–90		5		1				6
Total	232	122	43	12	88	2	0	499

or without a vasopressor. Twenty caudal blocks were performed using intracaine-hyaluronidase-epinephrine solutions. Many blocks were performed as shown by table 1. Hyaluronidase was used in all physical states as shown in table 3. Operations in many regions of the body were undertaken successfully (table 4). Data were recorded on the Chicago key-sort card, making data easily available. There was no

TABLE 4

OPERATIONS IN WHICH SOLUTIONS OF PONTOCAINE-HYALURONIDASE WITH OR WITHOUT A VASOPRESSOR WERE USED (THERAPEUTIC AND DIAGNOSTIC BLOCKS NOT INCLUDED)

Regions	No. of Op.	Actual Op. Time, hours		Actual Anes. Time, hours	
		Ave.	Max.	Ave.	Max.
Arm					
(a) Closed (fractures, etc.)	21	1	1½	1½	2
(b) Open (tendon repairs, grafts, amputations, etc.)	34	¾	5	1¾	5½
Breast					
(a) Radical mastectomy	2	2	2½	2½	3½
(b) Simple mastectomy	3	1¼	1¾	1¾	2¾
Abdominal					
(a) Extraperitoneal					
1. Hernia	21	½	1½	1	2¼
(b) Intraperitoneal					
1. Cholecystectomy	57	1¼	3	1¾	3¾
2. Colon resection	17	2	3½	2¾	4½
3. Gastric resection	33	2¼	4½	3	5
4. Incisional hernia	3	1	2	2½	3½
5. Miscellaneous	16	1	2	1½	2¾
6. Splenectomy		1¾	1¾	2¾	3
7. Whipple	3	2¼	4¼	3¼	5½
Leg					
(a) Closed (reductions and manipulations)	11	½	1¼	1	2
(b) Open (reductions, sequestrectomies, bunionectomies, etc.)	43	1	2½	1½	3½
Miscellaneous					
(a) Infiltration for lipomas, etc.	14	½	1¼	1	2¼
Neck and Face					
(a) Branchial cyst	5	1	2	1½	2¾
(b) Face (lip resections, fractured jaws, etc.)	14	½	3	1	3½
(c) Thyroidectomy	57	1½	1¾	1½	2½
(d) Radical neck dissections	1	1½	3½	2	4¼
Thorax					
(a) Intrapleural					
1. Intracostal blocks to supplement endotracheal anesthesia	3	2½	4¼	3½	5
Total	358				

screening of cases in this series. The discrepancy between the number of blocks and the number of patients occurred because some patients required more than one block.

Hyaluronidase 150 TRU (turbidity reducing units) was used in all solutions irrespective of the volume. It was thought that this amount of hyaluronidase should be adequate, since the current literature indicated that 150 TRU of hyaluronidase has been used successfully in clysis ranging from 150 cc. to 1000 cc.

Vasopressor solutions were added to the solutions in the form of epinephrine or neosynephrin. A small series of cases were run in which vasopressors were omitted from the anesthetic solution (table 5).

While it is recommended that hyaluronidase be used for subcutaneous injections only, most of the blocks performed entailed injections into muscle layers and deep fascial compartments. Care was taken to avoid intravascular injections, as hyaluronidase is measured in turbidity reducing units.

TABLE 5

COMPARISONS OF SOLUTIONS USED AS TO ONSET OF OPERATIVE AND POSTOPERATIVE ANALGESIA

Solution	Number of Cases	Time for Analgesia to Become Established from Completion of Block, minutes	Length of Time of Operative Analgesia, hours	Postoperative Analgesia, hours
Pontocaine (control)	224	10–45	4½–6	4–9
Pontocaine + vasopressor (control)	742	10–45	4½–6	4–9
Pontocaine + hyaluronidase	20	8–45	2 –2½	3–6
Pontocaine + hyaluronidase + epinephrine	408	8–15	4½–6	4–9
Pontocaine + hyaluronidase + neosynephrin	71	8–15	3½–4½	5–8

Before this series of cases was started we reported 1004 cases of nerve block and local infiltration analgesia in which pontocaine hydrochloride without hyaluronidase was employed (1). This series, therefore, will suffice as a control and references to it in the tables are marked "control." Our main purpose was to see if we could improve our percentage of satisfactory blocks. Comparable blocks were compared, explaining the discrepancy between 1004 cases mentioned above and the 966 shown in table 1.

With the exception of deep cervical block for thyroidectomy and intercostal with deep splanchnic blocks for upper abdominal surgical procedures, a satisfactory block is defined in our institution as one in which no supplementary or complementary anesthesia is needed other than the routine preoperative medication. In these two exceptions it is common for us to use nitrous oxide or 0.2 per cent sodium pentothal, or a combination of the two, as an analgesia. We prefer to use one of

these rather than excessive preoperative sedation because the postoperative period is less of a problem. It has been the observation at this clinic that in the two exceptions mentioned, no matter how adequate a block is performed, traction on the stomach, diaphragmatic irritation and tracheal manipulation cause physical and mental discomfort. No patient is allowed to suffer during a block analgesia. All of the patients in this series, as well as in the control series, were private patients. The large number of blocks is testimony to the fact that a high percentage of the blocks are satisfactory to both the patient and the surgeon.

In the 499 cases, twenty-three different regional blocks were performed (table 1). It will be noted that for many operations more than one block was required. Each operation, however, rather than each individual block was counted as a case. For example, a breast block for radical mastectomy includes a brachial block, intercostal block and superficial cervical block. This was counted as one anesthetic procedure, not three.

We employed two brands of hyaluronidase, diffusin and hydase; 400 cases were done with hydase and the remainder with diffusin.

RESULTS

Pontocaine-hyaluronidase-epinephrine or neosynephrin solutions were used to produce analgesia for general surgical procedures in 348 cases and for therapeutic and diagnostic procedures in 131 cases. Pontocaine-hyaluronidase was employed in 20 cases, including surgical, diagnostic and therapeutic procedures. Intracaine-hyaluronidase-epinephrine solutions were tried in 20 caudal blocks. Twenty-three types of nerve blocks in all parts of the body were done in the 499 cases so that any advantage or disadvantage of hyaluronidase might be detected (tables 1 and 4).

In local infiltration procedures such as removal of lipomas, breast biopsies, herniorrhaphy, circumcisions, trigger zone infiltrations, and ringing of the arm in conjunction with brachial block for operations above the elbow, hyaluronidase gave us approximately a 35 to 40 per cent increase in area of skin anesthesia. Skin wheals disappeared in thirty to sixty seconds, and the onset of operating analgesia was greatly shortened (table 5). After local infiltration with hyaluronidase-pontocaine solutions an area of erythema appears within three to six minutes and this area corresponds to the area of analgesia. If epinephrine or neosynephrin is used in the solution containing hyaluronidase, however, there is blanching rather than erythema and this area corresponds to the area of analgesia. These findings agree with the experimental work of Kirby, Echenhoff and Lobby (14).

Pontocaine-hyaluronidase-epinephrine solutions produced analgesia adequate for operating times of five to six hours, which is comparable to pontocaine-epinephrine solutions (table 5). Pontocaine-hyaluroni-

dase solutions gave operating times of three-fourths to two and one-half hours as compared to three and one-half to six hours with plain pontocaine solutions (table 5). Pontocaine-hyaluronidase-neosynephrin solutions gave operating times which were three and one-half hours to four and one-half hours (table 5).

TABLE 6

OVER-ALL PERCENTAGE OF SUCCESSFUL BLOCKS
(THERAPEUTIC, DIAGNOSTIC AND SURGICAL)

Nerve Block and Local Infiltration	Pontocaine-Hyaluronidase			Pontocaine (Control)		
	No. of Blocks	No. of Unsuc. Blocks	Satis. Blocks, per cent	No. of Blocks	No. of Unsuc. Blocks	Satis. Blocks, per cent
1. Brachial	52	2	96.2	272	10	96.4
2. Breast (Brachial, Superficial cervical, Intercostal $T_1 - T_9$)	5	0	100	9	0	100
3. Cervical (deep and superficial)	61	4	93	71	10	86
4. Hernia	21	2	90	37	7	81
5. Infiltration	24	2	94	18	2	88
6. Intercostal (bilateral) and deep splanchnic	129	6	95	85	14	84
7. Intercostal (bilateral and unilateral)	64	0	100	149	1	99
8. Lumbar sympathetic	35	0	100	19	0	100
9. Mandibular	3	0	100	10	0	100
10. Maxillary	2	0	100	5	0	100
11. Maxillary and mandibular	5	0	100	4	0	100
12. Maxillary, mandibular and deep cervical	2	0	100	1	0	100
13. Median, radial, ulnar (at wrist or elbow)	3	0	100	19	1	95
14. Mental	5	0	100	5	0	100
15. Obturator	3			2		
16. Paravertebral	6	0	100	31	0	100
17. Paravertebral (angina)	5	1	80	2	0	100
18. Sciatic and femoral	53	2	96	124	5	96
19. Splanchnic (deep)	3			5		
20. Stellate	10	0	100	95	0	100
21. Suprascapular	5			2		
22. Sciatic, femoral, obturator and lateral cutaneous	2	1	50	1	0	100
23. Transsacral (2,3,4)	1	0	100			
	499	20	96	966	50	95

Hyaluronidase did not significantly increase the over-all percentage of satisfactory diagnostic, therapeutic and surgical blocks (table 6). When surgical block procedures were separated from the above mentioned, the increase of successful blocks when hyaluronidase was employed was slight (table 7). As can be seen from these tables, hyaluronidase did not seem to be of any aid in increasing the percentage of successful anesthesias in the following blocks: brachial, breast, intercostal, lumbar sympathetic, mandibular, maxillary, median, ulnar, radial, mental, paravertebral, sciatic and femoral, stellate, transsacral,

or combinations of the above blocks. Hyaluronidase was a considerable aid in increasing the percentage of successful blocks from 81 to 94 in the following blocks or combinations of blocks: deep and superficial cervical, hernia, local infiltration, and intercostal-deep splanchnic (table 7). In the 20 caudal blocks, the percentage of successful blocks was not increased.

When hyaluronidase was incorporated in the anesthetic solution adequate blocks could be established with smaller volumes of anesthetic solutions.

TABLE 7

PERCENTAGE OF SUCCESSFUL BLOCK PROCEDURES IN SURGICAL PROCEDURES

Nerve Block and Local Infiltration	Pontocaine-Hyaluronidase			Pontocaine (Control)		
	No. of Blocks	No. of Unsuc. Blocks	Satis. Blocks, per cent	No. of Blocks	No. of Unsuc. Blocks	Satis. Blocks, per cent
1. Brachial	52	2	96.2	272	10	96.4
2. Breast (Brachial, Superficial cervical, Intercostal $T_1 - T_6$)	5	0	100	9	0	100
3. Cervical (deep and superficial)	61	4	93	71	10	86
4. Hernia	21	2	90	37	7	81
5. Infiltration	24	2	94	18	2	88
6. Intercostal (bilateral) and deep splanchnic	129	6	95	85	14	84
7. Mandibular	3	0	100	10	0	100
8. Maxillary	2	0	100	5	0	100
9. Maxillary and mandibular	5	0	100	4	0	100
10. Maxillary, mandibular and deep cervical	2	0	100	1	0	100
11. Median, radial, ulnar (at wrist or elbow	3	0	100	19	1	95
12. Mental (bilateral and unilateral)	5	0	100	5	0	100
13. Sciatic and femoral	53	2	96	124	5	96
14. Sciatic, femoral, obturator and lateral femoral cutaneous	2	1	50	1	0	100
	367	19	94.9	661	49	92.6

Hyaluronidase appears to be nontoxic to the tissues; no sloughs or areas of inflammation occurred in this series of cases. There were fourteen reactions to pontocaine-hyaluronidase solutions with vasopressors, and these deserve attention.

Three appeared to be directly caused by hyaluronidase. One occurred in a 40 year old woman who had a suprascapular nerve block with 25 cc. of a 0.25 per cent solution for an acute exacerbation of chronic bursitis. The block was uneventful but that night and the next day she complained of severe vaginitis. The patient was the wife of an excellent gynecologist so that there was no mistake in the diagnosis. Blocks with pontocaine-epinephrine solutions had been performed on this patient before and have been carried out since this particular block, without difficulty.

Two local vascular phenomena of intermittent skin areas of blanching and erythema in the region of the block were witnessed. One was in a superficial and deep cervical block and the area involved spread like a cape to the nipple line. The other occurred during a hernia block and spread 3 inches above the umbilicus and past the midline. Both of these disappeared in one-half hour without any noticeable change in the patient's condition.

Ten reactions to rapid absorption of pontocaine were noted. Six minimal pontocaine reactions characterized by drowsiness occurred during superficial and deep cervical block and 2 minimal reactions characterized by irregular heart rates, which returned to normal in ten minutes, occurred. In these 8 cases 90 cc. of 0.15 per cent pontocaine hydrochloride with 0.3 cc. of vasopressor and 150 TRU of hyaluronidase were employed. In 6 cases the vasopressor was neosynephrin and in 2 cases epinephrine.

The ninth reaction occurred in a 68 year old woman who had had an operation for acute cholecystitis under intercostal deep splanchnic block, employing 150 cc. of 0.1 per cent pontocaine solution with 0.3 cc. of epinephrine and 150 TRU of hyaluronidase. The operative procedure was uneventful. She was known to have cardiac disease and had a grossly irregular pulse before operation. The first day after operation a right therapeutic intercostal block was administered employing 50 cc. of 0.25 per cent pontocaine solution with 0.2 cc. of epinephrine and 150 TRU of hyaluronidase. Five minutes after the completion of the block she became irrational, blood pressure dropped from 124 to 86 mm. systolic and from 86 to 42 mm. diastolic, pulse was weak but retained the same irregularity as before the block, and the patient began to perspire and felt clammy. Apnea or convulsions did not occur. Oxygen was administered for fifteen minutes, and the patient recovered. She left the hospital in the usual time.

The tenth case of rapid absorption occurred in a 59 year old woman who two weeks previously had an uneventful cholecystectomy under intercostal deep splanchnic block, employing 150 cc. of 0.1 per cent pontocaine with 0.5 cc. of epinephrine and 150 TRU of hyaluronidase. After operation two right intercostal blocks were carried out uneventfully with 50 cc. of 0.25 per cent pontocaine with 0.3 cc. of epinephrine and 150 TRU of hyaluronidase. An elective subtotal thyroidectomy was scheduled and she received a superficial and deep cervical block, employing 90 cc. of 0.15 pontocaine with 0.3 cc. of neosynephrin and 150 TRU of hyaluronidase. Ten minutes after completion of the block she became cyanotic and had a convulsion lasting twenty seconds. Oxygen was administered under pressure and she responded without further treatment. Thyroidectomy was performed and her postoperative course was uneventful.

The last reaction, but by no means the one of least importance, occurred in a 55 year old man who had had a gastric resection for a

duodenal ulcer under nitrous oxide-oxygen-ether endotracheal anesthesia. He was severely deformed from arthritis and because of his deformity of the spine operation had to be performed with the patient in a sitting position. During his postoperative period a bilateral intercostal block was performed for pain, using pontocaine-epinephrine-hyaluronidase solution. At this time the blood pressure fell from 90 to 60 mm. systolic and from 50 to 0 mm. diastolic. He became cold and clammy but did not lose consciousness or become apneic. He left the hospital in the usual time. However, a pancreatic type of pain and the dumping syndrome developed. The surgeon asked us to do a sympathetic block of the fifth through the twelfth thoracic segments bilaterally. I refused his request twice because of the severe arthritis with poor landmarks and the patient's previous reaction to a block procedure. After the third request, however, the block was attempted with a volume of 90 cc. of 0.15 per cent pontocaine-hyaluronidase-epinephrine solution. No sedation was given but after severe pain occurred on the placing of the first two needles, sodium pentothal 0.6 per cent was given to the point of analgesia. At completion of the block, thirty minutes later, the patient ceased breathing. The blood pressure was 110 mm. systolic and 70 mm. diastolic; pulse 76 and respirations 18 at the beginning of the procedure. A quick check revealed no pressure or pulse. Oxygen was administered by endotracheal tube and other resuscitation drugs such as atropine and procaine were given intravenously. Cardiac massage was not attempted and the patient was pronounced dead one hour and fifteen minutes after cessation of breathing. Postmortem examination revealed nothing unusual. I believe this death was caused by a faulty injection, probably subdural, although the pathologist could find no puncture of the dura. The possibility of a sensitivity to pontocaine or hyaluronidase or the combination of the two must be considered. Nevertheless, I am hesitant to condemn either agent in view of the severe deformity of this patient.

DISCUSSION

The evaluation of hyaluronidase in regional analgesia is a difficult task. Many of our procedures require placement of the solutions deep in the tissues, and actual spread could not be determined. Block technics vary with the individual doctor as do the definitions of successful blocks. Our definition for a successful block was stated in a previous part of this paper. What constitutes a successful therapeutic or diagnostic block presents another problem. Stellate blocks were considered complete only if both a Horner's syndrome and an increase in temperature of the arm occurred. Lumbar sympathetic blocks were deemed satisfactory if the extremity in question became warm. If, however, this does not occur, all patients are given a subarachnoid block, and then if the extremity does not become warm, the block procedure is not condemned. Successful paravertebral, intercostal, transsacral, trigger

zone, and tic douloureux blocks are based on segmental sensory analgesia and the disappearance of pain. A satisfactory paravertebral thoracic sympathetic block for angina is based on a Horner's syndrome and relief of pain. Obturator, suprascapular, and deep splanchnic blocks are difficult to evaluate as much depends on subjective symptoms. These constitute only a small number and are not of significance in the over-all picture. Surgical blocks, such as brachial, sciatic, cervical, and so forth, seldom are required for therapeutic or diagnostic procedures, but when they are employed they are judged on sensory and motor loss as well as disappearance of pain. Using the above as criteria for blocks over the past two years, the over-all incidence of successful blocks at the clinic averages 94 to 95 per cent as shown by the control series (table 6). It should be stated here that we do not hesitate to perform a second block if the first attempt should fail. Pontocaine hydrochloride is the drug of choice in all block procedures. It permits starting the blocks one hour before the scheduled operating time with positive assurance that the analgesia established will be sufficient. This hour interval allows adequate time to observe the patient, and, if necessary, perform a second block.

TABLE 8

BLOCK PROCEDURE IN WHICH HYALURONIDASE PROVED TO BE OF VALUE

Nerve Block and Local Infiltration	Pontocaine-Hyaluronidase			Pontocaine (Control)		
	No. of Blocks	No. of Unsuc. Blocks	Satis. Blocks, per cent	No. of Blocks	No. of Unsuc. Blocks	Satis. Blocks, per cent
Cervical (deep and superficial)	61	4	93	71	10	86
Hernia	21	2	90	37	7	81
Infiltration	24	2	94	18	2	88
Intercostal (bilateral) and deep splanchnic	129	6	95	85	14	84
	235	14	94	211	33	81

Hyaluronidase did not alter the percentage of over-all successful blocks (table 6). The percentage of successful surgical blocks was improved an insignificant amount (table 7). When individual blocks were studied, however, it was found that hyaluronidase increased the percentage from 81 to 94 in four technics (table 8).

As stated previously, hyaluronidase can penetrate a fibrin barrier only if the drug is injected into it; otherwise, there is diffusion following the path of least resistance. On these premises it would not be expected that hyaluronidase would render a fascial plane permeable to an anesthetic solution. We found that it did not, and from the results obtained it can definitely be stated that fascial planes are effective barriers to solutions containing hyaluronidase. The following ex-

amples will prove this point. In 3 patients, in spite of paresthesias and analgesia of two of the three cords of the brachial plexus, hyaluronidase did not cause sufficient spread to produce a complete brachial block and these patients had to have a second block. It was also noted in hernia block that if the anesthetic solution was not placed accurately between the transverse and internal oblique fascia, the ilio-inguinal nerve was not anesthetized. Since similar examples could be noted for practically every block performed, the first concern of the anesthesiologist in nerve block analgesia is to place the needle correctly; otherwise, the diffusion properties of hyaluronidase will be of no avail.

In therepeutic and diagnostic technics, with the exception of local infiltration of trigger areas, there is no advantage in the spreading factor of hyaluronidase and in many such blocks it has a definite disadvantage. One of the most annoying complications of a stellate block, using the anterior approach, is accompanying temporary paralysis of the recurrent laryngeal nerve. When hyaluronidase was employed, the frequency of this complication increased 20 per cent, so hyaluronidase is no longer used. Also, when one contemplates removal or sectioning of nerves for pain relief or increase of circulation, spread of the anesthetic solution in diagnostic block may give a false impression. One of the complications of a lumbar sympathetic block is overflow and production of a bilateral sympathetic block from a unilateral approach. Hyaluronidase greatly enhances this chance.

Hyaluronidase was a definite help in four block procedures (table 8). Inguinal hernia, femoral hernia, and local infiltration blocks would be expected to benefit from a spreading factor, and they did. This was especially true in obese patients in whom distribution of local analgesic solutions in the subcutaneous fat is difficult. Intercostal deep splanchnic blocks for upper abdominal operations produced more satisfactory results than other blocks. No improvement was found or expected in the intercostal part of the technic, as the intercostal nerves lie within a fascial compartment which acts as a barrier unless the analgesic solution is properly placed. The celiac plexus in the deep splanchnic area, however, is especially adaptable to the spreading factor of hyaluronidase because it lies in the areolar tissue in the prevertebral space, and areolar tissue forms no barrier for the hyaluronidase. The nerves of the cervical plexus lie in connective tissue on the anterior surface of the transverse process between the anterior and posterior tubercle. If the needle is placed correctly on the anterior surface instead of on the posterior surface of the transverse process, hyaluronidase appears to give excellent spread to small volumes of solution. It should be noted here that one of the advantages of block analgesia for thyroidectomy is preservation of phonation, and hyaluronidase, by increasing spread of anesthetic solutions, increases the chances of involving the recurrent laryngeal nerve in the block if large volumes of solutions are placed around the fourth cervical nerve.

Hyaluronidase greatly shortens the effective analgesia of pontocaine hydrochloride solutions if a vasopressor agent is not added. This may be because of spread which results in rapid absorption (table 5). If epinephrine is added to the pontocaine-hyaluronidase solutions, the length of time of operative and of postoperative analgesia is comparable to that produced with pontocaine-epinephrine solutions (table 5). Solutions of pontocaine-hyaluronidase-epinephrine have been put to the test of actual operating times of four to six hours (table 4).

If neosynephrin is substituted for epinephrine, the length of time of surgical analgesia is somewhat shorter (table 5). We do not know whether this is due to the effectiveness of the neosynephrin or to the region of the block. A large number of this series occurred in cervical blocks. Since epinephrine substantially increases the pulse rate in thyrotoxicosis, we prefer to use neosynephrin. The neck is a very vascular structure and may absorb the solution more rapidly than other structures. Also, the increased metabolic rate may cause rapid metabolism of the pontocaine.

Hyaluronidase definitely shortens the period between completion of the block and the establishment of operating analgesia (table 5). It seems to enhance the penetrating power of the solution. We do not believe that the block is more profound but it surely becomes established more rapidly than when hyaluronidase is not employed.

While the drug companies recommend that hyaluronidase not be injected into deep tissues but used only subcutaneously, we have not found any contraindications to its use in regional analgesia which entails placement of solutions deep in the tissues. Solutions containing hyaluronidase have been injected intramuscularly and interfascially without difficulty. While all precautions have been observed to prevent intravascular injections of solutions containing hyaluronidase, it is hardly conceivable that it was avoided in this large series. Also, it is difficult to see why a small amount so dilute injected intravenously could cause great concern, even if its potency is measured in turbidity reducing units.

Twenty caudal transsacral anesthetics were administered, using 700 to 800 mg. of intracaine, 150 TRU of hyaluronidase, and 0.5 cc. of epinephrine. Normally caudal transsacral analgesia is established by the time the procedure is completed when intracaine is the anesthetic agent. Therefore, it did not appear that hyaluronidase was of any advantage.

Three of the toxic reactions reported would certainly seem to be an allergic type of response to hyaluronidase. Ten would seem to be due to the rapid absorption of the pontocaine solution, for instance, greater area, more rapid absorption. The last reaction cannot be blamed on either drug but must be explained on faulty technic or poor decision. Providing the usual concentrations and volumes of an anesthetic solution are employed, the addition of hyaluronidase increases

the chances of a toxic reaction to the local anesthetic agent or the vasopressor drug. We believe this to be true because, even though a vasopressor is incorporated in the solution to retard absorption, the spreading factor allows an increase up to 40 per cent in the normal anesthetized area. Therefore, applying rules of physics, the greater the surface, the more rapid the absorption. It would then be expected that the blood level of the local anesthetic agent and vasopressor drug would be higher than normal in a shorter period of time when hyaluronidase is added. To illustrate this point, if 90 cc. of a 0.15 per cent solution of pontocaine hydrochloride with a vasopressor and hyaluronidase is employed in a block, the blood level of pontocaine would be higher in a shorter period of time than if the same volume and percentage of pontocaine were used without hyaluronidase. Clinically this was found to be true. In the control series without hyaluronidase only one reaction to pontocaine occurred, while in this series there were ten which were referable to the anesthetic solution. Therefore, smaller volumes or more dilute concentrations or both should be administered when hyaluronidase is employed, if the blood level of the local agent and vasopressor drug is not to be increased.

At the present time the various brands of hyaluronidase cost the hospitals approximately one dollar per 150 TRU and the cost to the patient averages one dollar and eighty cents. Therefore, if the drug is not being used on an experimental basis, the cost in comparison to the advantage may not justify routine use.

At this clinic we found no difference between diffusin and hydase in this series.

CONCLUSIONS AND SUMMARY

Hyaluronidase is not a substitute for anatomical knowledge in regional analgesia.

Fascia, fascial planes and periosteum act as barriers to solutions containing hyaluronidase.

Addition of hyaluronidase to local anesthetic agents without epinephrine decreases the duration of analgesia.

If epinephrine is added to local anesthetic agents, hyaluronidase does not affect the analgesia time nor does the epinephrine affect the diffusion caused by hyaluronidase.

Therapeutic and diagnostic blocks are not aided by hyaluronidase and in some cases its use may give a faulty impression.

The interval between completion of a block and the establishment of operating analgesia is markedly shortened by administration of hyaluronidase.

Hyaluronidase was found to be useful in procedures involving infiltration of subcutaneous and areolar tissues, for instance, hernias, local infiltration and deep splanchnic blocks.

When hyaluronidase was incorporated in the anesthetic solution,

adequate blocks could be established with smaller volumes of anesthetic solutions.

There is no contraindication to infiltrating solutions containing hyaluronidase into deep tissues providing the normal precautions pertaining to intravascular injections are observed.

Hyaluronidase, 150 TRU, is effective in volumes of local anesthetic solution ranging from 110 to 150 cc.

Allergic reactions to hyaluronidase do occur.

Concentrations and volumes being equal, toxic reactions to local anesthetic agents and vasopressor drugs occur more frequently when hyaluronidase is added.

There was no advantage in using hyaluronidase in caudal analgesia.

At the present time, the cost of hyaluronidase compared to its value in regional analgesia may not justify routine use.

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