THE USE OF HYALURONIDASE IN LOCAL AND NERVE BLOCK ANALGESIA OTHER THAN SPINAL BLOCK: 1520 CASES *

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Received for publication November 24, 1950

REGIONAL analgesia is often a vital tool of the physician, and drugs, methods and technics that will facilitate its use have been sought for many years. Recent experimental and clinical work with hyaluronidase has clarified some of the factors controlling spread and absorption of solutions injected into the body tissues and has stimulated further research in this field (1–10). Hyaluronidase is now generally conceded to be the "spreading factor" of Duran-Reynals and McClean (11, 12). Its use in regional analgesia to effect a wider spread of the local anesthetic solution in the tissues was suggested by Duran-Reynals and Cosentino, although they did not record any experimental or clinical data (11, 13).

Many surgeons and anesthesiologists, in particular, avoid the administration of local infiltration and nerve block analgesia (except caudal and spinal) because they are unable to obtain satisfactory results in a high percentage of cases. Some authors have demonstrated that hyaluronidase increases by 40 per cent the normal area of skin analgesia resulting from intradermal injection of local anesthetic solutions when it is incorporated in the solutions (8). Therefore, it is obvious to the physician that if hyaluronidase can facilitate the spread of the local anesthetic solutions throughout all the body tissues to this extent, the incidence of satisfactory block from regional procedures might increase. Reports have appeared in the literature on the use of hyaluronidase in regional analgesia, spinal block excluded (8). A previous paper based on the first 519 cases in this series, has been published, and the growing interest in the use of hyaluronidase in local anesthetic solutions prompted this re-evaluation of our clinical data (14). Our main purpose in studying this series was to see if we could improve the percentage of satisfactory blocks.

* Hyaluronidase was supplied by Ortho Pharmaceutical Corporation and Wyeth, Incorporated. Pontocaine hydrochloride was furnished by Winthrop-Stearns, Inc.

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ESSENTIAL PHARMACOLOGY OF HYALURONIDASE

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 injected solutions. The rate of diffusion is proportionate to the amount of enzyme, and the extent is proportionate to the volume of solution (2, 7).

Hechter found that the natural hyaluronic acid barrier was partly restored in twenty-four and completely restored in forty-eight hours (15).

Therapeutic doses of hyaluronidase are nontoxic and the ratio of toxicity to the therapeutic dose is 200,000 to 1 (16). Hyaluronidase has no effect on body temperature or the kidney, and in clinical use there has been no evidence of toxic or allergic reaction (2, 4, 5, 15). Solutions containing hyaluronidase can penetrate a fibrin barrier only if injected into it; otherwise, the drug diffuses around it and follows the path of least resistance (7).

Amounts of hyaluronidase are measured in turbidity reducing units i.e., T.R.U.

PROCEDURE

The procedure employed was the same as that reported in the first 519 cases and briefly consists of the following salient points (14):

1. Patients of all ages, physical status and operative risk, without screening, for whom nerve blocks were advocated received local anesthetic solutions containing hyaluronidase (tables 1 and 2).
2. Pontocaine hydrochloride was the local anesthetic agent employed in all cases except the 20 caudal cases in which intracaine was used.
3. This series with hyaluronidase is compared to a series of 966 nerve blocks in which pontocaine solutions without hyaluronidase was administered (17).
4. The series without the hyaluronidase will be referred to as the "control series." The volumes and concentrations of the local anesthetic agents and the vasoconstrictor drugs for the control series and this series were comparable for the same procedures except for the addition of hyaluronidase; that is, 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 or without a vasopressor.

TABLE 1

TYPES OF NERVE BLOCKS PERFORMED

Nerve Blocks Performed	Pontocaine-Hyaluronidase*			Pontocaine Control*		
	No. of Therap. Diagnos. Blocks	No. of Surg. Blocks	No. of Pts.	No. of Therap. Diagnos. Blocks	No. of Surg. Blocks	No. of Pts.
1. Brachial	2	236	228	2	270	245
2. Breast (Brachial) (Superficial cervical) (Intercostal T1–T9)		25	24		9	8
3. Cervical (deep and superficial)	5	95	100	4	67	71
4. Hernia		33	33		37	37
5. Infiltration (local)	28	37	53		18	18
6. Infra-orbital		4	4			
7. Intercostal (bilateral) and deep splanchnic		354	342	2	83	85
8. Intercostal (bilateral and unilateral)	275	3	180	141	8	87
9. Intracapsular (knee or shoulder)		2	2			
10. Lateral femoral cutaneous	1		1			
11. Lateral femoral cutaneous and femoral	1		1			
12. Lumbar sympathetic	79		30	19		12
13. Mandibular		15	15	1	9	10
14. Mandibular and deep cervical		9	9			
15. Maxillary		6	6	4	1	2
16. Maxillary—mandibular	2	6	8		4	4
17. Maxillary, mandibular, and deep cervical		3	3		1	1
18. Median, radial, ulnar (at wrist or elbow)		9	9		19	19
19. Mental	1	8	9		5	5
20. Obturator	4		4	2		2
21. Paravertebral	20	3	21	22	9	28
22. Paravertebral (angina)	5		4	2		2
23. Sciatic and femoral	5	167	170	5	119	124
24. Splanchnic (deep)	7		7	5		4
25. Stellate	10		10	95		47
26. Suprascapular	23		19	2		2
27. Sciatic, femoral, obturator and lateral femoral cutaneous		14	14		1	1
28. Transsacral	1		1			
29. Ulnar	1	1	2			
	470	1030	1309	306	660	814

* With and without a vasoconstrictor drug.

5. 150 T.R.U. of hyaluronidase was used in solutions in this series irrespective of the volumes and concentrations of the local anesthetic solutions (table 3).

6. With the exception of deep cervical block for thyroidectomy and intercostal with deep splanchnic blocks for upper abdominal surgical procedures, a satisfactory block for a surgical procedure is defined in our institution as one in which no supplementary or complementary

TABLE 2

PHYSICAL STATUS RECORD

Age Group, years	American Society Anesthesiology Code 1	2	3	4	5	6	7	Total
0–10	3	1			4			8
11–20	36	11	1		14			62
21–30	92	28	1		20			141
31–40	143	55		1	18			217
41–50	172	124	10	3	52			361
51–60	136	162	17	4	46			365
61–70	74	124	26	6	28	2		260
71–80	8	41	18	1	10			78
81–90		6	1	1				8
	664	552	74	16	192	2		1500

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 analgesic. We prefer to use one of these rather than excessive preoperative sedation. It has been the observation at this clinic that in the two exceptions mentioned, no matter how adequately a block is performed, traction on the stomach, diaphragmatic irritation and tracheal manipulation cause physical and mental discomfort. No patient is allowed to "suffer through" a surgical procedure executed under 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 are satisfactory both to the patient and the surgeon.

7. The complete block necessary for the operation, rather than each individual block, was counted as a procedure. For example, a wrist block includes a medial, radial and ulnar block with an intradermal and

TABLE 3

PERCENTAGE COMPARISONS

Pontocaine, per cent	No. of Cases	Dosage Used				Reactions	
		Max., cc.	Max., mg.	Av., cc.	Av., mg.	Pontocaine Hyaluronidase + Vasoconstrictor	Pontocaine + Vasoconstrictor (Control)
0.1	313	250	250	150	150	0	0
0.15	279	110	165	85	125	9	0
0.20	91	100	200	60	125	0	0
0.25	738	100	250	50	125	8	1
0.3	64	40	120	40	100	0	0
0.4	11	30	120	30	120	0	0
0.5	4	40	200	10	50	0	0

subcutaneous wristlet block. This was counted as one anesthetic procedure, not four.

8. Vasopressor solutions were added to the solutions in the form of epinephrine or neosynephrine. Twenty cases in this series were performed in which vasopressors were omitted from the anesthetic solution.

9. We employed two brands of hyaluronidase: diffusin in 1120 and wydase in 400 cases.

10. Data were recorded on the Chicago key-sort card, making data easily available.

RESULTS

In the 1520 procedures in which hyaluronidase was incorporated in the local anesthetic solution, 29 different types of blocks were performed (table 1). There were 816 males and 704 females in this series. The discrepancy between the number of patients and the number of cases occurred because many patients having therapeutic and diagnostic blocks required more than one block. A large variety of operations in various parts of the body were performed (table 4).

Pontocaine-hyaluronidase-epinephrine or neosynephrine solutions were used to produce analgesia for surgical procedures in 1020 cases and for therapeutic and diagnostic procedures in 460 cases. Pontocaine-hyaluronidase was employed in 20 cases, including surgical, diagnostic and therapeutic procedures. Intracaine-hyaluronidase-epinephrine solutions were tried in 20 caudal blocks.

In local infiltration procedures such as for removal of lipomas, breast biopsies, herniorrhaphy, circumcisions, infiltration of trigger zones, 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 neosynephrine 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 Looby (8).

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-hyaluronidase 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-neosynephrine solutions gave operating times which were three and one-half hours to four and one-half hours (table 5).

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, the increase of successful blocks by employing hyaluronidase 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

TABLE 4

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

	No. of Operations	Actual Operating Time		Actual Anesthesia Time	
		Av.	Max.	Av.	Max.
Arm					
(a) Closed (fractures, etc.)	76	1	1½	1½	2
(b) Open (tendon repairs, grafts, amputations, etc.)	163	¾	5	1¾	5½
Breast					
(a) Radical mastectomy	22	2	2½	2½	3¼
(b) Simple mastectomy	3	1¼	1¾	1¾	2¾
Abdominal					
(a) Extraperitoneal					
1. Hernia	39	½	1½	1	2¼
(b) Intraperitoneal					
1. Cholecystectomy	178	1¼	3	1¾	3¾
2. Colon resection	25	2	2½	2¾	4¼
3. Gastric resection	98	2¼	4¼	3	5
4. Miscellaneous	30	1	2	1½	2¾
5. Splenectomy	2	1¾	1¾	2¾	3
6. Whipple	7	2¼	4¾	3¼	5½
7. Secondary closure	14	1	2	2¼	3¼
Leg					
(a) Closed (reductions and manipulations)	45	½	1¼	1	2
(b) Open (reductions, sequestrectomies, bunionectomies, etc.)	149	1	2½	1½	3½
Miscellaneous					
(a) Infiltration for lipomas, etc.	25	½	1¼	1	2¼
Neck and Face					
(a) Branchial cyst	11	1	2	1½	2¾
(b) Face (lip resections, fractured jaws, etc.)	40	½	3	1	3½
(c) Thyroidectomy	91	1½	1¾	2	2½
(d) Phrenic nerve crushes	1	1	1	1½	1½
(e) Radical neck dissections	1	1½	3½	2	4¾
Thorax					
(a) Intrapleural					
1. Intracostal blocks to supplement endotracheal anesthesia	10	2½	4¼	3½	5
Total	1030				

TABLE 5

COMPARISONS OF SOLUTIONS USED AS TO ONSET OF ANALGESIA, OPERATING ANALGESIA AND POSTOPERATIVE ANALGESIA

Solution	Number of Cases	Time for Analgesia to be 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	8–15	¾–2½	3–6
Pontocaine + hyaluronidase + epinephrine	1375	8–15	4½–6	4–9
Pontocaine + hyaluronidase + neosynephrine	105	8–15	3½–4½	5–8

above blocks. Hyaluronidase was a considerable aid in increasing the percentage of successful blocks 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.

Hyaluronidase appears to be nontoxic to the tissues; no sloughs or areas of inflammation occurred in this series of cases. There were seventeen reactions to pontocaine-hyaluronidase-epinephrine or neosynephrine, and these deserve attention (table 8).

Three appeared to be directly caused by hyaluronidase. These may be summarized as follows:

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.

In two other patients, 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.

Thirteen reactions of rapid absorption of pontocaine were noted. These may be summarized as follows:

Nine minimal pontocaine reactions characterized by drowsiness occurred during superficial and deep cervical block. A combination of 90 cc. of 0.15 per cent pontocaine hydrochloride with 0.3 cc. of neosyneprine and 150 T.R.U. of hyaluronidase was employed. No treatment was administered for these reactions other than careful watchful expectancy.

Two minimal pontocaine reactions characterized by irregular heat rates were noted. These returned to normal in ten minutes with-

TABLE 6

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

Nerve Blocks Performed	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	238	9	96	272	10	96
2. Breast (Brachial) (Superficial cervical) (Intercostal T1–T9)	25	2	92	9	0	100
3. Cervical (deep and superficial)	100	6	94	71	10	86
4. Hernia	33	3	91	37	7	81
5. Infiltration (local)	65	4	94	18	2	88
6. Infra-orbital	4	0	100			
7. Intercostal (bilateral) and deep splanchnic	354	17	95	85	14	84
8. Intercostal (bilateral and unilateral)	278	0	100	149	1	99
9. Intracapsular (knee or shoulder)	2	0	400			
10. Lateral femoral cutaneous	1	0	100			
11. Lateral femoral cutaneous and femoral	1	0	100			
12. Lumbar sympathetic	79	0	100	19	0	100
13. Mandibular	15	1	93	10	0	100
14. Mandibular and deep cervical	9	1	88			
15. Maxillary	6	0	100	5	0	100
16. Maxillary—mandibular	8	0	100	4	0	100
17. Maxillary, mandibular, and deep cervical	3	0	100	1	0	100
18. Median, radial, ulnar (at wrist or elbow)	9	0	100	19	1	95
19. Mental	9	0	100	5	0	100
20. Obturator	4			2		
21. Paravertebral	23	2	91	31	0	100
22. Paravertebral (angina)	5	1	80	2	0	100
23. Sciatic and femoral	172	5	97	124	5	96
24. Splanchnic (deep)	7			5		
25. Stellate	10	0	100	95	0	100
26. Suprascapular	23			2		
27. Sciatic, femoral, obturator, and lateral femoral cutaneous	14	3	79	1	0	100
28. Transsacral	1	0	100			
29. Ulnar	2	0	100			
	1500	54	95	966	50	96

TABLE 7

PERCENTAGE OF SUCCESSFUL BLOCK PROCEDURES IN SURGICAL PROCEDURES

Nerve Blocks Performed	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	236	8	96	270	10	96
2. Breast (Brachial) (Superficial cervical) (Intercostal T1–T9)	25	2	92	9	0	100
3. Cervical (deep and superficial)	95	6	94	67	10	85
4. Hernia	33	3	91	37	7	81
5. Infiltration	37	2	95	18	2	88
6. Infra-orbital	4	0	100			
7. Intercostal (bilateral) and deep splanchnic	354	17	95	83	13	84
8. Intercostal (bilateral) and unilateral	3	0	100	8	0	100
9. Intracapsular (knee or shoulder)	2	0	100			
10. Mandibular	15	1	93	9	0	100
11. Mandibular and deep cervical	9	1	88			
12. Maxillary	6	0	100	1	0	100
13. Maxillary—mandibular	6	0	100	4	0	100
14. Maxillary, mandibular, and deep cervical	3	0	100	1	0	100
15. Median, radial, ulnar (at wrist or elbow)	9	0	100	19	1	95
16. Mental	8	0	100	5	0	100
17. Paravertebral	3	0	100	9	0	100
18. Sciatic and femoral	167	5	97	119	5	96
19. Sciatic, femoral, obturator and lateral femoral cutaneous	14	3	79	1	0	100
20. Ulnar	1	0	100			
	1030	48	95	660	48	93

out treatment, one following a sciatic and femoral block and the other following a brachial block. In these two cases 90 cc. of 0.15 per cent pontocaine hydrochloride and 150 T.R.U. of hyaluronidase with 0.3 cc. of epinephrine was injected.

One 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 c.c. of epinephrine and 150 T.R.U. 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 T.R.U. of hyaluronidase. Five minutes after the completion of the block she became irrational; blood pressure dropped from 124 to 86 mm. systolic and 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.

One case of rapid absorption occurred in a 59-year-old woman who two weeks previously had an uneventful cholescystectomy under intercostal deep splanchnic block, employing 150 cc. of 0.1 per cent pontocaine with 0.5 cc. of epinephrine and 150 T.R.U. 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 T.R.U. 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 neosynephrine and 150 T.R.U. 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.

TABLE 8

BLOCK PROCEDURES 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)	95	6	94	67	10	85
Hernia	33	3	91	37	7	81
Infiltration	37	2	94	18	2	88
Intercostal (bilateral) and deep splanchnic	358	17	95	83	13	84
	523	28	94	205	32	84

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 endothraceal anesthesia. Because of severe arthritic deformity of the spine the 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. A pancreatic type of pain and the dumping syndrome, however, developed. The surgeon asked us to do a sympathetic block of the fifth through the twelfth thoracic segments bilaterally. We 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. We 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 a combination of the two must be considered. Nevertheless, we are 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 physician as do the definitions of successful blocks. Our definition for a successful operative 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 and dry. If, however, this did not occur, all patients were given a subarachnoid block, and then if the extremity did not become warm and dry, the block procedure was 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, that is, 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 96 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 because of its prolonged duration of analgesia. 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, time to perform a second block.

Hyaluronidase did not alter the percentage of over-all successful blocks (table 6). The percentage of successful surgical blocks was improved by an insignificant amount (table 7). When individual blocks were studied, however, it was found that hyaluronidase increased the percentage from 84 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 be stated with some certainty that fascial planes are effective barriers to solutions containing hyaluronidase. The following examples will prove this point. In 3 patients, in spite of paresthesias and analgesia of two of the three cords of the brachial plexus, hyaluranidase 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 ilioinguinal 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 therapeutic and diagnostic technics, with the exception of local infiltration of trigger areas, there is no advantage in the spreading factor of hyaluronidase; in fact, in many such blocks it has a definite disadvantage. One of the most annoying complications of a stellate block, using the anterior approach, is the 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 in this block. Also, when one contemplates removal or sectioning of nerves for pain relief or increase of circulation, the extensive spread of the anesthetic solution in the tissue may give a false impression of the surgical prognosis. 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 danger.

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 with hyaluronidase. 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. Therefore, when executing this block, we perform the intercostal blocks first and then add the hyaluronidase to the local anesthetic solution for the celiac plexus block. 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-hyaluranidase solutions, the length of time of operative and 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).

Until the last two months of this study, it was routine for us to substitute neosynephrine for the epinephrine in our cervical blocks with pontocaine-hyaluronidase solutions. This was done because epinephrine tended to increase the pulse rate of thyrotoxicotic patients even though they were controlled with iodine or propylthiouracil or both. We noted in these cases that the anesthetic time was somewhat shorter. We do not know whether this is because neosynephrine is less effective as a vasoconstrictor in local anesthetic solutions than epinephrine, to the region blocked, or to the underlying disease. The neck is a very vascular structure for its size and may absorb the solution more rapidly, or the increased metabolic rate in the thyrotoxicotic patient may cause rapid metabolism of the pontocaine. During the past two months we have eliminated hyaluronidase from the local anesthetic solutions for cervical plexus block because nine of the thirteen reactions caused by rapid absorption of the local anesthetic drug occurred in this block. It is interesting to note that during the past two months our number of successful cervical blocks has not decreased with the omission of hyaluronidase from the local anesthetic solution nor has the anesthetic time varied. Therefore, we can only draw the following conclusions:

1. The most important step in any regional procedure is determining anatomic relations and correct placement of the needles.
2. The efficiency of the regional anesthesiologist improves as the same block is repeatedly executed.
3. Hyaluronidase may be a help to the occasional regional anesthesiologist or to the anesthesiologist who is just learning regional technic in increasing the number of his successful blocks.

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.

Although 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 entailing placement of solutions deep in the tissues. Solutions containing hyaluronidase have been injected intramuscularly and interfascially without difficulty. While all precautions were observed to prevent intravascular injections of solutions containing hyaluronidase, it is hardly conceivable that it was avoided in this large series. It is difficult, also, to see why a small amount so dilute injected intravenously could cause great concern.

Twenty caudal transsacral anesthetics were administered, using 700 to 800 mg. of intracaine, 150 T.R.U. 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. It did not appear that hyaluronidase was of any advantage, since neither the onset nor the adequacy of the analgesia was affected.

Three of the toxic reactions reported would noticeably seem to be allergic types of response to hyaluronidase. Thirteen would seem to be the result of the rapid absorption of the pontocaine solution. 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 the rule 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 thirteen which were referable to the anesthetic drug. 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 are relatively expensive. 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 wydase in this series.

CONCLUSIONS AND SUMMARY

Hyaluronidase is not a substitute for anatomic 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 infiltrations 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 T.R.U., is effective in volumes of local anesthetic solution ranging from 10 cc. to 150 cc.

Allergic reactions to hyaluronidase may 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 in every block procedure.

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