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Prevention of Thromboembolic Complications with Miniheparin-Dihydroergotamine in Patients Undergoing Lumbar Disc Operations

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Summary. We have evaluated the incidence of bleeding complications using miniheparin(2 × 2500 IU daily)-dihydroergotamine starting preoperatively in a randomized, controlled, prospective, double-blind study in 50 patients undergoing herniated lumbar disc operations. There was no difference in the incidence of intraoperative bleeding problems between the two groups. Preoperatively, 13 patients have been treated in another hospital with conventional low-dose heparin, and of these 13 patients, 7 developed bleeding complications. There were two deep wound hematomas in the placebo group. Early removal of stitches or operative revision of the wound was not necessary in either group. We conclude that the use of minidose heparin-dihydroergotamine is feasible for the prevention of thromboembolic complications in patients undergoing herniated lumbar disc operations, since an increased incidence of bleeding complications was not observed. This preventive method should therefore be further clinically evaluated.

Key words: Lumbar disc – Heparin – Thromboembolism – Dihydroergotamine

Introduction

In contrast to other fields of surgery, postoperative bleeding complications in neurosurgery are more often connected with catastrophic sequelae [1] and all drugs interfering with the clotting mechanism are avoided. Patients with herniated lumbar discs are often bedridden in the preoperative phase, and it is known that immobilisation is an important factor in the development of thromboembolic complications [7]. In this group of patients there are many younger and middle-aged persons with no malignant disease, and in such patients thromboembolic complications must be avoided by all means. It is therefore of interest to know if it is possible to use drugs which have been proven to be effective in other fields of surgery for the prevention of thromboembolic complications in neurosurgery and especially in patients undergoing lumbar disc operations. A dosage of 2 × 2500 IU heparin mixed with 0.5 mg dihydroergotamine (DHE) has been shown to reduce the incidence of thromboembolic complications in general surgery without producing dangerous bleeding complications. Using such a regimen, the incidence of bleeding complications was lower as compared to 5000 IU heparin 2 or 3 × daily [2, 5, 9, 11, 12]. However, neurosurgical patients have not so far been studied. In a randomized, prospective, controlled double-blind study we have therefore evaluated 50 patients undergoing lumbar disc operations for the incidence of bleeding complications under minidose heparin-DHE. Deep vein thrombosis and pulmonary emboli were diagnosed by objective means only if there were clinical signs for such complications. We did not intend to prove the effectiveness of minidose heparin-DHE for the prevention of thromboembolic disease, such studies are already available [4, 5, 9, 10, 11, 12].

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Patients and Methods

We included 50 adult patients undergoing lumbar disc operations, excluded were those with recurrent disease, epidural compression by metastases and patients with abnormal preoperative clotting tests. Using the closed envelope technique, the patients were randomized into two groups of 25 patients each, receiving either 2500 IU heparin-DHE twice daily or placebo. A computer-produced randomization list was used. The first injection was given 2 h preoperatively s.c. in an abdominal skin fold. Postoperative administration was carried out at 12 hourly intervals for at least 7 days or until the patient left hospital, if this was earlier. Surgeons were allowed to continued administration after the 7th day if the clinical situation made this necessary.

At the end of each operation, the surgeon was asked if there had been increased bleeding. All wounds were inspected daily during hospital stay for superficial or deep hematomas, and a note was made if removal of stitches, or operative revision of the wound, or drain insertion was necessary. The amount of blood drained into the vacuum bottles was measured. If there was clinical suspicion of deep vein thrombosis, a phlebogram, plethysmography, Doppler ultrasound or an I^{125} fibrinogen test was performed. Patients suspected of having a pulmonary embolism received a chest X-ray, ECG, perfusion ventilation scintigram or a pulmonary angiogram. All drugs administered during the 10 days before and the 7 days after operation were noted. During the first 24 h neurological examination was carried out every 3 h.

Laboratory Examinations. Clotting analysis was first performed preoperatively, and then 30 min after beginning of the

operation: prothrombin time (normal 70%–120%), activated partial thromboplastin time (<35s), thrombin time (13–21s), thrombocyte count (150–400 × 10^3). Bleeding time was measured according to Ivy preoperatively and on the 6th postoperative day.

Results

In total 25 patients each were accorded to the placebo or the heparin-DHE group (Table 1); 5 patients in the placebo and 4 in the heparin-DHE group were admitted to the trial by error, they showed preoperative changes in the clotting mechanism. In this rather interesting group of patients there were 5 bleeding complications, 4 of these 5 patients received 5000IU of heparin 2 or 3 × daily in another hospital. However, the bleeding complications were not of such a severe nature to cause the surgeons to alter the protocol. One of the patients in the placebo group had a deep vein thrombosis on the 5th postoperative day, confirmed by phlebography and an I^{125} fibrinogen test. In all other patients the postoperative course was uneventful.

Table 1 shows furthermore that the two groups of patients were strictly comparable as regards sex, age in years, body weight, number of days in hospital and number of postoperative days. In the placebo group 11 patients did not show any intra- or postoperative bleeding complications and had normal clotting mechanisms preoperatively; 3 of these patients had received low-dose heparin elsewhere preoperatively, but did not show any coagulation changes whatsoever. One patient showed a prolonged postoperative bleeding time with values of 11.5–16.5min for unknown reasons. All other parameters studied were within the normal range.

In the heparin-DHE group 14 patients did not show any intra- or postoperative bleeding problems. Of these, 2 have received preoperative low-dose heparin elsewhere, and 1 of them showed a prolonged prothrombin and thrombin time. All other parameters studied were within the normal range.

Bleeding Complications

As Table 2 shows, the number of bleeding complications in both groups was similar. In neither group was there early removal of stitches or operative revision of the wound.

Table 1. Number and details of patients wrongly or correctly admitted to the study

	Placebo	Heparin-DHE
n admitted	25	25
n preoperative changes in clotting mechanisms	5	4
n correctly admitted	20	21
n males	13	12
n females	7	9
Age in years (mean ± SD)	44.5 ± 9.7	47.4 ± 13
Body weight in kg (mean ± SD)	72.8 ± 13.7	73.1 ± 14.5
n days in hospital (mean ± SD)	12.3 ± 2.8	12.7 ± 3
n postoperative days (mean ± SD)	10.5 ± 2.2	10.8 ± 2.6

Table 2. Bleeding and thromboembolic complications

	Placebo	Heparin-DHE
n increased *intraoperative* bleeding	7	6
n deep wound hematoma	2	0
n vacuum drainage	13	16
more blood in suction bottle than normal	2	1
ml blood in vacuum bottle	70 ± 27	82 ± 51
Protocol broken		
due to increased intraoperative bleeding	0	2
due to suspected deep hematoma formation	1	0
due to suspected deep vein thrombosis (not confirmed)	0	1
due to suspected pulmonary embolism	0	1
n deep vein thrombosis		
suspected	2	3
confirmed	0	1
n pulmonary embolism		
suspected	0	2
confirmed	0	0

In 1 patient in the placebo group, the protocol was broken because there was a suspicion of a deep postoperative hematoma on the 4th postoperative day. The patient complained of severe pain and myelography was compatible with hematoma formation. However, the pain disappeared spontaneously. In 2 patients in the heparin-DHE group, the protocol was also broken: during both operations the surgeon felt that bleeding was more than normal and protamine was given, 1 of the patients had received low-dose heparin during the 10 days before operation. Both patients had an uneventful postoperative course. Ten patients in the placebo and 8 in the heparin-DHE group had pre- and postoperative drugs which could possibly influence the clotting mechanism, however no correlation was found. Tables 3 and 4 show all patients with any sort of bleeding complications from both groups correlated to their values from the clotting tests. In the placebo group, 2 patients had received low-dose heparin before operation, 1 of these showed a prolonged prothrombin and thrombin time intraoperatively, and 1 additional patient had an intraoperative prolonged prothrombin time. In the heparin-DHE group no clinically relevant hematomas were found. Again 1 patient had received low-dose heparin elsewhere in the week preoperatively. Even though the intraoperative clotting tests were normal, the surgeon felt that this patient was bleeding abnormally and broke the protocol. The postoperative course was uneventful.

Thromboembolic Complications (Table 2)

In the placebo group 2 patients were clinically suspected of having a deep vein thrombosis. However, in both cases objective tests revealed no signs of deep vein thrombosis. In the heparin-DHE group deep vein thrombosis was suspected in 3 patients; in 1 the diagnosis was confirmed by a fibrinogen test and phlebography. This was the same patient who had receiv-

Table 3. Coagulation parameters in patients with bleeding complications in placebo group

Patient no.	♀/♂	Bleeding complication	Protocol broken	Protamine HCl given	Preoperative					Intraoperative			Post-oper. BT	Pre-operative drugs
					PTT	APTT	TT	T	BT	PTT	APTT	TT		
7	♀	H	No	No	94	29	20	337	0 0 1.5	*66*	33	17	1 1.5 1	Piroxicam
16	♀	B	No	No	74	27	16	385	2.5 0.5 2.5	*66*	25	*22*	2.5 6 3.5	LDH
20	♂	H	Yes	No	82	30	16	268	0 2.5 1	87	30	16	2.5 5 0	–
24	♂	B + R	No	No	92	26	16	248	1.5 0 2	71	32	17	0 0 0	Mefenamic acid
29	♂	B	No	No	89	27	15	245	3 5 3	73	24	14	0 0.5 4.5	–
34	♂	B	No	No	82	27	18	408	2.5 0.5 1	86	27	16	2.5 0 0	LDH
40	♂	B + R	No	No	92	25	14	253	0 2.5 0.5	81	26	14	*6.5* *6.5* 7	–
45	♂	B	No	No	91	27	16	147	0.5 0 0	77	27	16	0 0 0	–
47	♂	B	No	No	97	29	16	–	0 0.5 0.5	86	30	18	0 0 0.5	–

B: increased intraoperative bleeding
H: deep hematoma in operation wound
R: draining more blood than normal into suction device
PTT: prothrombin time (100% = normal)
APTT: activated partial thromboplastin time in s
TT: thrombin time in s
T: thrombocyte count $\times 10^3$
BT: bleeding time in min
LDH: low-dose heparin

ed protamine intraoperatively for increased bleeding and postoperatively he did not receive heparin-DHE. In the other 2 patients objective tests revealed no deep vein thrombosis. There were also 2 suspect cases of pulmonary embolism, but again objective diagnosis was negative.

Discussion

It is certainly fair to say that routine low-dose heparin prevention is not carried out throughout the world for patients undergoing prolapsed lumbar disc operations, the main reason being the fear of bleeding complications. Powers and Edwards [13] in their recent review state that they saw approximately 5 to 10 fatal postoperative pulmonary emboli among 1000 patients operated upon in the neurosurgical service at the University of California, San Francisco, each year. This confirms our own experience which quite clearly shows that severe, even fatal pulmonary embolism is possible after elective neurosurgical procedures. Barnett [3] has demonstrated the safety of low-dose heparin for elective neurosurgical procedures. Cerrato [6] used a complicated and cumbersome method measuring plasma heparin concentrations. He observed no increased hematoma formation studying intracranial operations only. This method is however not widely used.

But not only in neurosurgery is the fear of bleeding complications the main argument against the use of a systemic prevention with low-dose heparin. This fact produced a number of studies which all showed that low-dose heparin in combination with DHE is equally effective in reducing the incidence of thromboembolic complication as a higher dose of heparin alone, but the concomitant risk of bleeding complications is definitely lower [2, 5, 9, 11, 12]. These findings encouraged us to try the combination of heparin-DHE in neurosurgical patients. In this initial pilot study, we concentrated on lumbar disc operations as a standard model. The 9 patients who should not have been admitted to the trial revealed most interesting results. They all had preoperative changes in their coagulation mechanism because they had received standard

Table 4. Coagulation parameters in patients with bleeding complications in heparin-DHE group

Patient no.	♀/♂	Bleeding complication	Protocol broken	Protamine HCl given	Preoperative					Intraoperative			Postoper. BT	Preoperative drugs
					PTT	APTT	TT	T	BT	PTT	APTT	TT		
2	♂	B	No	No	96	24	17	302	–	76	25	19	0.5 1.5 2	–
3	♂	B	No	No	82	28	17	346	–	80	27	17	3 1.5 0.5	
12	♀	B	Yes	Yes	88	27	16	193	6.5 0 1.5	77	27	15	–	–
17	♀	R	No	No	94	26	18	–	4 3.5 1	71	27	17	1 3.5 5.5	–
23	♂	B	No	No	>100	27	14	–	1 1 1	87	31	16	0 1 0.5	–
27	♀	B	Yes	Yes	78	24	14	237	0.5 2 0.5	76	24	17	–	LDH
39	♂	B	No	No	92	24	14	331	0 0 0	–	–	–	2.5 5.5 4.5	–

B: increased intraoperative bleeding
H: deep hematoma in operation wound
R: draining more blood than normal into suction device
PTT: prothrombin time (100% = normal)
APTT: activated partial thromboplastin time in s
TT: thrombin time in s
T: thrombocyte count $\times 10^3$
BT: bleeding time in min
LDH: low-dose heparin

low-dose heparin in a dosage of 5000 IU 2 to 3 × daily in other hospitals. Eventually it was discovered that 8 further patients had received low-dose heparin elsewhere, thus of 13 patients who had received low-dose heparin preoperatively, 7 showed increased bleeding in the intra- and postoperative course. This confirms previous findings, assuming a heparin pool in the human body. Hellgren [8] showed this quite nicely, administering the heparin as an aerosol.

As a foremost practical conclusion, we recommend every neurosurgeon to make sure that his patients have not had low-dose heparin *before* operation, since this definitely increases the chance of bleeding complications. On the other hand, we can conclude from our small trial that the administration of a miniheparin-DHE regimen is feasible and possible since in this double-blind study no increased bleeding was observed which made operative revision or early removal of stitches necessary. In none of the patients receiving heparin-DHE were there any hematomas near the spinal canal. In no case was there any neurological deterioration postoperatively, and we feel that this combination should be further tested clinically in other fields of elective and emergency neurosurgery. We say this, knowing that peripheral vasospastic reactions have been described after administration of heparin-DHE. The etiology of this complication is still unclear, it seems to be extremely rare, the incidence being 1:50,000. Everybody working with heparin-DHE should be aware that such peripheral vasospastic reactions can occur; if they do, administration has to be stopped and intravenous nitroprusside and calcium antagonists are the drugs of choice for treatment. Definitely the advantages of the combination outweigh the few side effects. Alternative methods using mechanical devices are now available [14], however it must be stressed that in contrast to low-dose heparin, heparin-DHE and dextran, these mechanical devices have never been shown to effectively reduce the incidence of fatal pulmonary emobli in surgical patients. We therefore feel that only the use of drugs which have been proven to be effective in other fields of surgery should be used before further large clinical prospective, randomized, controlled studies confirm the safety and practicability of mechanical devices.

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