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Effect of Indomethacin on Postoperative Protein Metabolism After Gastrectomy Under Total Parenteral Nutrition

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Abstract: A randomized trial was undertaken to evaluate the effects of postoperative indomethacin (IDM) administration on protein metabolism in 20 patients who underwent an uncomplicated distal gastrectomy and were placed on postoperative total parenteral nutrition (TPN). Ten patients (the IDM group) received 50 mg of IDM every 8 h after operation up to postoperative day (POD) 4 while the other ten patients (the control group) received neither IDM nor any other non-steroidal anti-inflammatory drug, postoperatively. Though the requirement for postoperative plasma transfusion was significantly greater in the IDM group, the albumin level on POD 1 was significantly lower in this group than in the control group. The postoperative changes of C-reactive protein, retinol binding protein, and pre-albumin between the two groups showed no difference. Moreover, the urinary 3-methylhistidine excretion, N-balance, and plasma aminogram on POD 4 also demonstrated no difference. We thus concluded that postoperative IDM administration after elective surgery has no additional anti-catabolic effect on the presence of TPN.

Key Words: indomethacin, protein metabolism, total parenteral nutrition, gastrectomy

Introduction

The muscles are one of the target organs which, under various stressful conditions, provide amino acids which are taken up in the liver for protein synthesis and glyconeogenesis.[1–3] The degradation of muscle is mediated by various factors, such as counter-regulatory hormones,[4–6] interleukin-1,[7] and proteolysis-inducing factor.[1] Since indomethacin (IDM), an inhibitor of cyclooxygenase which is a key enzyme for prostaglandin (PG) synthesis, can inhibit muscle degradation in sepsis[3,8] and improve nitrogen loss after surgery,[9,10] PG (PGE_2) may be a final mediator in the control of muscle degradation.[7,11] It is therefore reasonable to use IDM postoperatively to suppress unnecessary muscle wasting provided that a sufficient amount of amino acids can be supplied from an external source for hepatic utilization. However, since IDM is known to inhibit protein,[3] RNA,[12] and DNA synthesis,[2] the routine use of IDM in the postoperative period can not be fully approved. Asoh et al.[10] reported that postoperative nitrogen loss and endocrine responses are suppressed by IDM administration, but in their study they did not state the effect of IDM on protein production or the influence of postoperative hypocaloric nitrogen-free nutrition. Since starvation stimulates protein degradation,[13–15] the effect of IDM may be strongly affected by the postoperative nutritional status. Thus, this study was designed to evaluate the postoperative use of IDM and its effects on protein production and muscle catabolism in patients given short-term total parenteral nutrition (TPN) after uncomplicated surgery in order to prevent hyponutrition and to provide a source of amino acids.

Patients and Methods

Preoperatively, gastric cancer patients scheduled to undergo a radical distal gastrectomy were randomly allocated into two groups. Patients in either a poor nutritional state, high operative risk, or under steroid treatment were excluded. Informed consent was obtained for participation. The control group received neither IDM nor any other non-steroidal anti-inflammatory agents after operation up to postoperative day (POD) 4, and fever was controlled by cooling with ice, when necessary. The IDM group received a suppository containing 50 mg IDM at 8 h intervals beginning immediately after surgery and continuing up to POD 4. In all

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patients, the TPN access route was secured during anesthesia and a fixed regimen of TPN (200 g of glucose, 100 g of fructose, 50 g of xylitol, and 60 g of amino acid containing 33.5% branched chain amino acids in 1,800 ml/day) was prescribed from 10:00 a.m. on POD 1 to 10:00 a.m. on POD 4. No lipid emulsion was infused. For postoperative pain relief, an epidural catheter through which buprenorphine hydrochloride (0.1 mg) was injected every 12 h immediately after operation up to POD 4, was introduced before anesthesia. An additional dose could be administered if the patient required it.

A total of 26 patients were enrolled in this study, 6 of whom were excluded for the following reasons: 1 had a lesion which was later histologically found to be benign, 1 received a different TPN regimen, 2 received postoperative steroids to control preexisting diseases (systemic lupus erythematous, acute intermittent porphyria), and 2 underwent different surgical procedures. As a result, 20 patients were included in the study, with 10 patients in each group. The histologic stages of gastric cancer in each group were as follows: stage 1, 6 cases; stage 2, 1 case; stage 3, 2 cases; and stage 4, 1 case (IDM group); and stage 1, 8 cases; and stage 3, 2 cases (control group). No postoperative complications were observed in these patients throughout the study period. During the operation, the decision regarding the necessity for blood (citrated whole blood) or plasma (plasma protein fraction containing 4.4% albumin) transfusion was made by the anesthesiologist. After the operation, the need for plasma was determined by the physician in charge to maintain the serum albumin at more than 3.5 g/dl. Food intake was started on POD 4. The following parameters were monitored preoperatively (POD −1) as well as on POD 1, POD 4, and POD 7: Serum total protein, albumin, C-reactive protein, pre-albumin, and retinol binding protein. Plasma aminogram was measured on POD −1 and POD 4. A 24 h urine sample was collected and the measurement of 3-methylhistidine and urea N was carried out from POD −1 through POD 4.

Within each study group, the data were analyzed by Student's paired *t*-test. Comparisons between the two study groups were made by an analysis of variance using Dunnett's *t*-test and χ^2 analysis. Differences were considered significant at a P value of less than 0.05.

Results

The profiles of the 20 enrolled patients are summarized in Table 1. All characteristics were fairly comparable in the two groups. The amounts of transfused blood and plasma in each group are listed in Table 2. The transfusion of blood and plasma was not prohibited and the decision for administering postoperative plasma transfusion was made by the physician in charge, who was not involved in this study. During operation (POD 0), the amounts of transfused blood and plasma were almost identical in the two groups. In contrast, the amount of plasma transfused postoperatively and the frequency of transfusion were strikingly different.

Table 1. Patient profiles

	IDM group (n = 10)	Control group (n = 10)
Sex: male/female	6/4	7/3
Age (years)	56.7 ± 10.5	57.1 ± 10.1
Weight (kg)	55.1 ± 10.0	57.7 ± 10.2
Operation Time (min)	212.5 ± 35.0	222.5 ± 46.5
Blood Loss (ml)	469 ± 317	401.5 ± 317

Data are expressed as mean ± SD
IDM, Indomethacin

Table 2. Amounts of transfused blood and plasma

Group	Transfusion	Postoperative days 0	1	2	3	4	5	6	7
IDM group n = 10	Blood[a]	800							
	Cases[b]	2							
	Plasma[a]	2,550	1,600	750	1,800	1,450	900	500	500
	Cases[b]	6	3	3	4*	4*	3	1	1
Control group n = 10	Blood[a]	1,100							
	Cases[b]	1							
	Plasma[a]	2,750	800	500	0	0	0	0	0
	Cases[b]	6	2	1	0	0	0	0	0

Data are expressed as mean ± SD
* $P < 0.05$ vs the control group using the χ^2 analysis
[a] Total amount of blood (citrated whole blood) or plasma (plasma protein fraction containing 4.4% albumin) administered in each group
[b] Number of patients who received either blood or plasma on each individual day

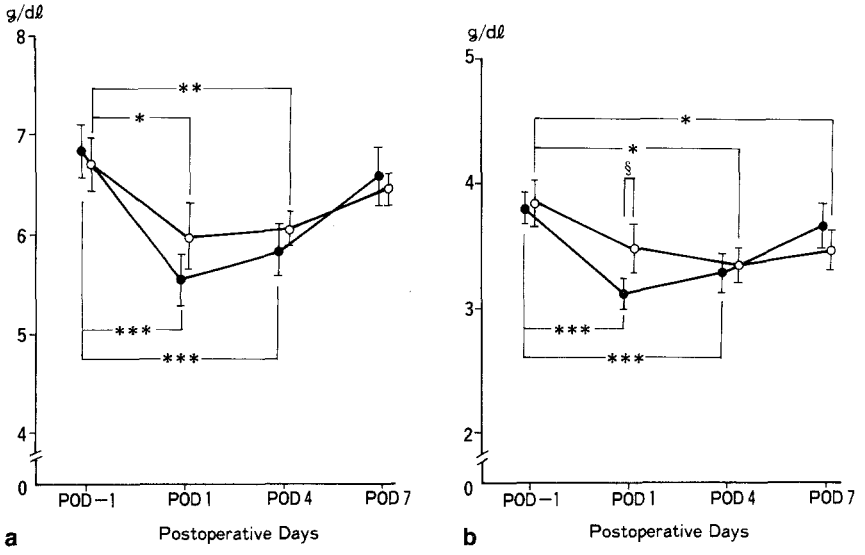

Fig. 1a,b. Postoperative changes in total protein and albumin: Serum protein (**a**) and albumin (**b**) were serially monitored perioperatively in the control (*open circles*) and the IDM (*closed circles*) groups. Data are expressed as mean ± SD. $^{*1}P < 0.05$, $^{*2}P < 0.01$ $^{*3}P < 0.001$ vs POD −1, using the Student's paired *t*-test, § < 0.05, the control vs the IDM groups, by an analysis of variance using Dunnett's test

On POD 3 and POD 4, four patients required mean amounts of 450 and 363 ml of plasma transfusion in the IDM group while none required transfusion in the control group.

Protein Production

The changes in total protein and albumin are shown in Fig. 1. The decreases in total protein on POD 1 and POD 4 were significant in both groups compared to the values on POD −1. Likewise, the decrease in albumin on POD 1 and POD 4 in the IDM group and on POD 4 and POD 7 in the control group were significant versus the values on POD −1. In spite of the greater amount of plasma transfused in the IDM group versus the control group, the level of total protein tended to be lower on POD 1 (5.51 ± 0.51 vs 5.96 ± 0.62 g/dl, $P < 0.1$) and the level of albumin on POD 1 was significantly lower (3.11 ± 0.27 vs 3.47 ± 0.43 g/dl; $P < 0.05$) in the IDM group than the corresponding levels in the control group.

The postoperative changes in rapid turnover proteins, pre-albumin and retinol binding protein, are shown in Fig. 2. The pre-albumin levels on POD 1 and POD 4 decreased significantly in both groups compared with the level on POD −1, but no difference was found between the two groups. Likewise, the levels of retinol binding protein on POD 1 and POD 4 decreased significantly in comparison with that on POD −1 in both groups, but again no difference was found between the two groups. The change in C-reactive protein, an acute phase protein, was also monitored. It increased significantly on POD 1 and POD 4 in both groups but no difference was found between the two groups on POD 1 and POD 4 (7.3 ± 3.63 on POD 1 and 7.7 ± 3.24 ng/ml on POD 4 in the IDM group; 5.7 ± 1.87 on POD 1 and 7.8 ± 3.76 ng/ml on POD 4 in the control group).

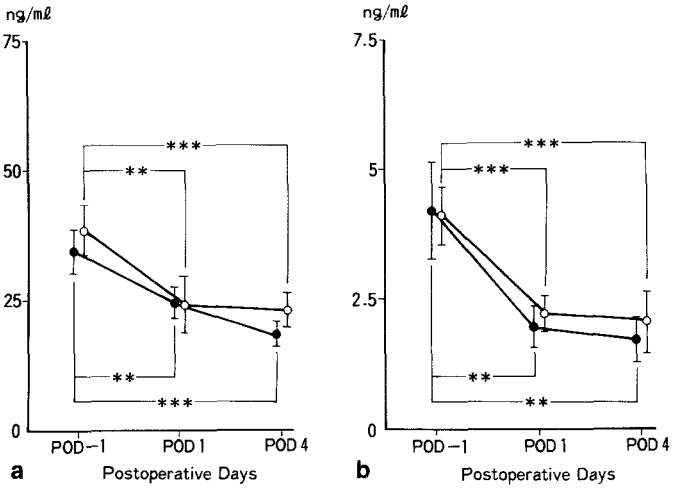

Fig. 2a,b. Postoperative changes of rapid turnover proteins: Serum pre-albumin (**a**) and retinol binding protein (**b**) were serially monitored perioperatively in the control (*open circles*) and the indomethacin (*IDM*) (*closed circles*) groups. Data are expressed as means ± SD. $^{**}P < 0.01$, $^{***}P < 0.001$ vs POD −1, using the Student's paired *t*-test.

Muscle Catabolism

Muscle catabolism was monitored using urinary 3-methylhistidine excretion and N-balance as listed in Table 3. No significant difference was found between the two groups in 3-methylhistidine, the most commonly employed marker for muscle degradation, or in the N-balance. A plasma aminogram was measured on POD −1 and POD 4. In the IDM group, the levels of serine (120.4 ± 13.1 vs 90.3 ± 11.9 n mol/ml), glutamine

Table 3. Urinary 3-methylhistidine excretion and N-balance

3-Methylhistidine or N-balance	Group	Postoperative days (POD)				Cumulative Amount POD 1–3
		−1	1	2	3	
3-Methylhistidine (mmol/day)	IDM $n = 10$	177 ± 78	211 ± 47	207 ± 54	171 ± 59	589 ± 103
	Control $n = 10$	164 ± 54	243 ± 101	221 ± 89	189 ± 65	622 ± 209
3-Methylhistidine/ creatinine ratio (μmol/mg creatinine)	IDM $n = 10$	189 ± 50	177 ± 37	187 ± 35	183 ± 37	
	Control $n = 10$	187 ± 39	182 ± 28	196 ± 38	213 ± 38	
N-balance (mg/kg per day)	IDM $n = 10$	−147.4 ± 52.7	−25.4 ± 42.7	−18.2 ± 41.6	14.4 ± 55.3	−29.2 ± 105.9
	Control $n = 10$	−161.3 ± 47.6	−43.5 ± 66.0	1.1 ± 38.2	24.3 ± 60.6	−18.1 ± 127.9

Data are expressed as mean ± SD

(549.0 ± 87.2 vs 352.0 ± 64.1), citrulline (32.0 ± 9.4 vs 14.7 ± 6.1), asparagine (43.8 ± 6.4 vs 21.7 ± 6.0), tyrosine (66.5 ± 16.8 vs 49.2 ± 9.3), and cysteine (48.8 ± 10.4 vs 13.8 ± 7.6) decreased, as well as the levels of threonine (110.8 ± 16.3 vs 140.5 ± 32.2), methionine (21.6 ± 4.2 vs 37.9 ± 7.3), valine (209.3 ± 36.9 vs 295.7 ± 48.2), leucine (122.7 ± 22.3 vs 199.4 ± 42.6), isoleucine (58.7 ± 9.4 vs 99.0 ± 22.2) and phenylalanine (62.3 ± 8.9 vs 111.2 ± 17.9) increased on POD 4 in comparison with the levels on POD −1. In the control group, the levels of serine (129.0 ± 11.4 vs 104.9 ± 20.3), asparagine (49.4 ± 8.3 vs 25.9 ± 6.4), glutamine (606.7 ± 73.9 vs 335.4 ± 130.4), citrulline (31.0 ± 6.2 vs 15.4 ± 3.9), alanine (387.2 ± 49.5 vs 307.4 ± 59.4), cysteine (49.2 ± 10.1 vs 18.4 ± 5.6), methionine (27.8 ± 4.7 vs 38.8 ± 6.4), and tyrosine (69.6 ± 12.3 vs 55.6 ± 8.6) decreased, and the levels of valine (250.0 ± 42.9 vs 293.5 ± 37.0), isoleucine (74.3 ± 14.3 vs 93.2 ± 14.1), leucine (151.7 ± 27.1 vs 189.5 ± 29.0), and phenylalanine (70.6 ± 12.9 vs 110.9 ± 9.3) increased on POD 4 in comparison with levels on POD −1. No difference in the plasma concentrations of the respective amino acids was found between the two groups.

Discussion

Skeletal muscle cells synthesize several PGs, e.g., PGE_2, $F_2\alpha$, and I_2, which in turn affect muscle protein metabolism. For instance, $PGF_2\alpha$ activates muscle protein synthesis and PGE_2 activates muscle protein degradation.[16,17] However, the role of PGE_2 in muscle protein catabolism has generated a good deal of controversy among investigators.[7,8,17–19] Tian and Baracos[8] reported that prostaglandin-dependent muscle wasting occurs during infection in both the broiler chick and the laboratory rat. In contrast, Hasselgren and Fischer reported[18,19] that PGE_2 does not regulate either total or myofibrillar protein breakdown in incubated muscles from either normal or septic rats. The reasons for these conflicting results may stem from diverse experimental methods, drugs used to suppress PG synthesis, and parameters of muscle protein catabolism. In one clinical study, IDM improved postoperative nitrogen loss via decreased endocrine responses in elective gastrectomy.[10] A similar nitrogen-sparing effect of a cyclooxygenase inhibitor was found postoperatively following abdominal surgery in dogs via a reduced efflux of amino-nitrogen and phenylalanine from the muscle.[9] On the other hand, caution is still urged because IDM inhibits protein synthesis in the muscle and liver in septic rats,[3] protein and RNA synthesis in myoblasts,[12] and DNA synthesis in the liver.[20] Considering these conflicting effects of IDM on protein synthesis and catabolism, one has to therefore be prudent regarding its clinical application. Up to now, there has been no clinical study evaluating the combined effects of IDM administration following uncomplicated surgery done with adequate nutritional support. Therefore, the present study was conducted to clarify the effect of IDM in the presence of postoperative TPN in elective abdominal surgery.

A plasma aminogram may reflect a balance between the release from skeletal muscles and uptake by visceral organs. In the present study, significant changes of amino acid concentrations were found after operation in both the control and the IDM groups, such as increase of phenylalanine, which is a useful marker of muscle breakdown,[9] and a decrease of glutamine indicating increased utilization. Since the administration of IDM did not cause any difference in the plasma aminogram, IDM may thus have little effect on muscle

breakdown and protein synthesis in the present situation. Though the postoperative albumin level was suppressed, IDM did not affect the levels of C-reactive protein or rapid turnover proteins. It has been reported that ibuprofen, a cyclooxygenase inhibitor, attenuaties the metabolic response, i.e., the increase of corticotropin, cortisol, and catecholamines, which occurs in endotoxin injected humans[21] as well as in bacteremic dogs[22] but does not affect acute phase responses, i.e., elevation of C-reactive protein, protein catabolism, leukocytosis, and hypoferremia. The synthesis of acute phase proteins and the production of rapid turnover proteins may thus be regulated by factors other than the initiation of PG formation. In contrast to previous reports,[9,10] muscle catabolism, monitored by urinary 3-methylhistidine excretion and N-balance, was not affected by IDM, indicating that PGs have no direct effect on muscle degradation in elective surgery when sufficient nutrients are provided.

It is interesting to note the influence of nutrition on the action of IDM because most in vivo experiments,[3,8,9] as well as at least one clinical study,[10] which have reported an anti-catabolic effect of IDM were conducted under fasting or hypocaloric conditions. Recently, Hasselgren et al.[13] observed that in the muscles of fasted rats, thyrosine release, a marker of proteolysis, is increased by the addition of septic plasma, although 3-methylhistidine is not affected. In contrast, these phenomena do not take place in the muscles of non-fasted rats. Since nutrition itself counteracts the effect from the catabolic stimulus, an anti-catalytic effect of IDM was not evident in this study. Glucocorticoids are known to be responsible for muscle degradation,[5,6] the effect of which is evident in the muscles of fasted animals presumably because of the associated enhancement of glyconeogenesis in the liver.[23] IDM not only attenuates the increase in cortisol under conditions of stress[21,22] but also may inhibit the activation of a non-lysosomal ATP-dependent proteolysis during fasting.[15] Thus, in a non-fasted condition, the effect of glucocorticoids in the muscles is not evident[23] and the inhibition of IDM on the activation of proteolysis may be limited.

In conclusion, IDM treatment in uncomplicated post-gastrectomy patients receiving TPN decreased postoperative albumin levels but had no effect on muscle catabolism. No beneficial effect of IDM was therefore found following abdominal surgery when sufficient nutrition was provided.

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