Original Article

Successful treatment of surgical abdominal wounds complicated by multiple bowel fistulas with a combination of total parenteral nutrition, hyaluronan-iodine complex and delayed surgery: results of a monocentric experience

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ABSTRACT: ***Background:*** *Abdominal catastrophe, suture leakage and wound dehiscence are serious complications of surgical procedures. Wound infection is a frequent complication and the mortality is high due to long and difficult treatment procedures. Treatment is often difficult as a result of fistula formation, presence of necrotic and infected tissue, and complex surgical management. Long-term nutritional support is necessary between treatment periods. We have developed a new healing system which is based on the combination of hyaluronan and iodine. This system has been successfully used in our department for more than 4 years. The aim of this observational study was to assess the effect of this complex in subjects with abdominal catastrophe.*
Methods: *Seven patients with multiple fistulas and extensive wound dehiscence were admitted to our metabolic care unit. Total parenteral nutrition (TPN) providing full coverage of nutritional needs was used in all cases until full recovery of oral nutrition. After removal of necrotic tissue the wounds were dressed once daily with sterile gauze soaked in hyaluronate-iodine complex (Hyiodine®). Intestinal fistula secretions were drained using negative pressure. After wound granulation and improvement of patient condition (no sooner than after 2 months) the intestinal fistulas were resected and intestinal continuity established. Then, when primary suture was impossible, the hyaluronan-iodine complex was again used for healing of the open abdominal wound.*
Results: *TPN and hyaluronan-iodine treatment led to significant wound healing in all patients. Within 14 days all wounds were dirt free and covered with granulation tissue. After 3.3±0.9 months, patients were operated on (fistula resection and anastomosis). The abdominal wall was not closed surgically in 4 patients during fistula resection. However, local treatment with hyaluronan-iodine complex led to complete wound healing in all patients within 4-10 weeks.*
Conclusions: *We obtained excellent results with the sodium hyaluronate-iodine complex in combination with TPN in the treatment of complicated abdominal wounds. We presume this effect is related to the combination of immune cell activation, angiogenic properties, and a strong affinity of hyaluronate to water together with the antimicrobial effect of iodine. (Nutritional Therapy & Metabolism 2008; 26: 177-83)*

KEY WORDS: Intestinal fistula, Postoperative care, Total parenteral nutrition, Wound dehiscence, Wound healing, Hyaluronate

INTRODUCTION

Multiple intestinal perforations with fistula formation and open abdomen are frequent causes of the so-called abdominal catastrophe. The treatment of abdominal catastrophe is complex and time consuming. It includes treatment of infection complications, drainage of potential abscesses and intestinal fistulas, nutrition support and treatment of possible metabolic complications. In spite of this complex treatment, the open abdomen with multiple fistulas is a common result. Moreover, massive visceral swelling, abdominal wall defect and intraabdominal infection (abscess or peritonitis) may pose an extreme surgical challenge. Dynamic-retention su-

tures were used in similar patients after trauma, vascular reconstruction, tumor extirpation, and intraabdominal infection (1). However, the presence of intestinal fistulas limits their use. Additional surgical procedures such as skin grafting or plastic surgical reconstruction of the abdominal wall are also difficult in patients with intestinal fistulas (2). As the wound is often infected, a modification of the surgical treatment combined with a medical approach might improve the outcome of patients. Nonsurgical treatment of complicated abdominal catastrophe consists mainly of systemic antibiotic therapy and local management based on frequent wound dressing. Vacuum-assisted therapy has also been successfully used in recent years (3). Final abdominal wall reconstruction is possible only after treatment of all infectious foci and intestinal fistulas; however, a simple, safe and universal method for local treatment is neither widely used nor known.

Hyaluronic acid (HA) is a nonsulfated glycosaminoglycan, which is an integral part of the extracellular matrix. It is a linear polysaccharide with repeating disaccharide units composed of glucuronic acid and N-acetyl glucosamine. In particular, it forms the backbone for the organization of proteoglycans (4). Early response to tissue injury includes the formation of a temporary matrix rich in hyaluronan and fibrin, which aids the influx of fibroblasts and endothelial cells to the wound site, and the subsequent formation of granulation tissue (5).

A unique characteristic of HA, related to its variable functions, is its hydration capacity. It contains approximately 1000-fold more water than polymer saccharide when hydrated. In this respect HA is the most hydrophilic molecule occurring in the human body. The hydrophilic nature of HA creates an environment suitable for the migration of cells to new tissue sites and offers protection to cells and extracellular matrix molecules, which can have a beneficial effect on the healing of both acute and chronic wounds (5). HA also facilitates morphogenesis in the neonatal period and is probably an important molecule for organ-regenerative processes. A rapid increase in the concentration of HA sets the stage for reorientation and differentiation of cells to allow regrowth of the forelimbs of newts. An increase in HA in the microenvironment promotes the organization of connective tissue at the wound site (6). Many cell surface receptors for HA have been detected on various types of cells and tissues. This structural relationship could explain the effect of HA on cellular activities such as migration and phagocytosis (7).

Because of the ubiquitous nature of HA, its solutions would appear to be useful in bandaging difficult wounds. HA was tested as an aid in wound healing, but the results were not convincing. We therefore use a mixture of iodine with hyaluronate (Hyiodine®, CPN, Dolni Dobrouc, Czech Republic) to inhibit its bacterial degradation and improve its healing capacity. We found this complex very effective in the bandaging of infected and difficult wounds (8). Currently, we are unaware of any other studies that have assessed the results of this type of therapy in patients with complicated abdominal wounds. Therefore we decided to study its effect in patients with abdominal catastrophe.

MATERIAL AND METHODS

Seven patients with multiple intestinal fistulas and large abdominal wound dehiscences were treated at the Metabolic Unit of the Department of Metabolic Care and Gerontology, Medical Faculty, Charles University, Hradec Kralove, Czech Republic. The characteristics of the patients are shown in Table I. Informed consent was obtained from each patient according to the Helsinki Declaration of 1975.

All patients were operated on several times at various regional hospitals in the Czech Republic. However, all surgical procedures (often repeated) were complicated by the development of multiple intestinal fistulas, open abdomen and systemic inflammation. Intestinal fluid leakage to the peritoneal cavity was apparent in all patients at the time of admission to our department.

After admission, all patients received total parenteral nutrition (TPN) by central venous catheter. According to the protocol defined for these patients at our department they received 34 Kcal, 4.5 g glucose, 0.8 g lipid emulsion and 2 g amino acid solution per kg of body weight per day. Electrolytes, vitamins and trace elements were an integral part of TPN.

Secretions from fistulas were drained using negative pressure. Necrotic tissue was partially removed; entire debridement was not possible due to the risk of multiple intestinal injury and perforations. Therefore the only local treatment of infected abdominal dehiscence was based on daily dressing with hyaluronan-iodine complex gauze and careful intestinal drainage. Patients received TPN and intravenous fluid replacement. Intravenous antibiotic therapy was administered during the first 2-3 weeks. This treatment was continued for 2-5 months until improvement of local status and patient's general condition. Then reconstruction of intestinal continuity was performed in all patients. All intestinal fistulas were resected and subsequent multiple intestinal anastomoses were completed during one surgical procedure. However, the abdominal cavity could not be closed in 4 patients because the tension was too great to physically permit fascia and skin reapproximation.

Wound dressing protocol

The dressing of each abdominal wound was changed daily. The sterile gauze was immersed in hyaluronan-iodine complex (Hyiodine®) and this saturated gauze was wrapped round the entire wound surface including the intestine. Several layers of sterile dry gauze covered the gauze layers saturated in hyaluronan-iodine. This dressing was held in place using tape. When the surface cover of the dressing was wet, the outer layers of gauze were replaced with new layers of sterile dry gauze. However, the gauze that was immersed in hyaluronan-iodine and was in direct contact with the wound surface stayed in place for 24 hours. The process of wound healing was monitored by one observer (LS) and pictures of the wounds were regularly taken until healing was complete (Camedia – Olympus). The results included time to operation, time to complete wound closure, and reported complications associated with the use of the dressing.

RESULTS

Combination of TPN, fistula suction and local treatment led to significant clinical improvement before the final reconstructive procedure. Hyaluronan-iodine was used as the only dressing in all patients. Its moisture-retentive and antiadhesive properties were very efficient. The dressing was usually changed every 24 hours. The upper gauze layers were changed 2-3 times daily because of wound secretion during the first 2 weeks of treatment. Then the whole bandage was changed once a day only. No adherence of gauze to the wound bed was evident in our group of patients.

During 2 weeks of careful intestinal suction, local therapy and TPN all wounds were dirt free and showed growth of new granulation tissue. Throughout the next 2-5 months the nutritional and metabolic status of the patients improved; muscle force and mental activity also improved considerably. Then final surgery was performed in all patients (Tab. II). Intestinal fistulas were

TABLE I - STUDY GROUP

Patient	Age (years)	Sex	Disease	Intestinal complications	
1	66	M	Perforated gastric ulcer	8 intestinal fistulas	Wound dehiscence, stercoral peritonitis
2	72	F	Perforated sigmoid diverticulitis	4 intestinal fistulas	Wound dehiscence, stercoral peritonitis, necrotizing fasciitis
3	48	F	Complication of gynecological operation	4 intestinal fistulas, short bowel	Wound dehiscence, sepsis, peritonitis
4	75	M	Mesenteric embolization	2 intestinal fistulas, short bowel	Wound dehiscence and peritonitis
5	69	M	Sigmoid cancer resection	6 intestinal fistulas	Wound dehiscence, diffuse peritonitis
6	62	M	Acute pancreatitis	2 intestinal fistulas	Wound dehiscence, retroperitoneal phlegmon
7	64	F	Sigmoid cancer resection	4 intestinal fistulas	Wound dehiscence, severe bleeding

M, male; F, female

TABLE II - RESULTS OF TREATMENT

Patient	Time to surgical treatment of intestinal fistulas (months)	Time to complete wound healing after surgery (weeks)	Comment
1	5	10	Open abdomen after second operation
2	2	3	Abdominal wall closure during fistula surgery
3	3	2	Abdominal wall closure during fistula surgery
4	3	4	Open abdomen after second operation
5	3	4	Open abdomen after second operation Plastic surgery
6	4	3	Abdominal wall closure during fistula surgery
7	3	5	Open abdomen after second operation
Mean	3.3	4.9	
Standard deviation	0.9	2.2	
Median	3.0	4.0	

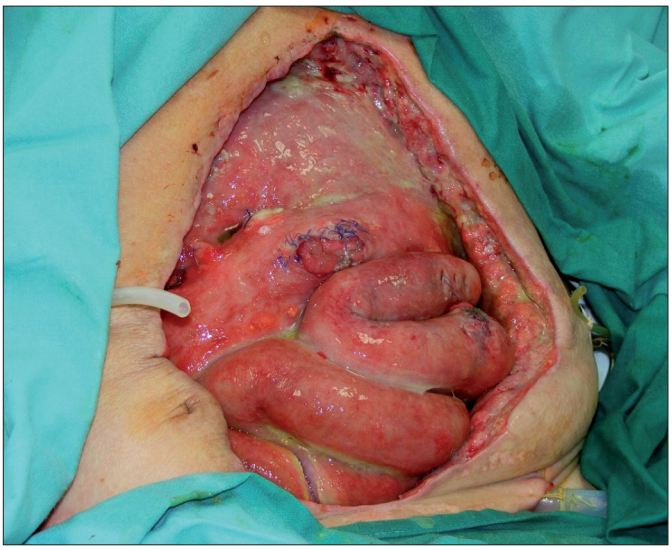

Fig. 1 - *A 66-year-old man with a large abdominal wound after complicated gastric resection and subsequent reoperations in a local hospital. Result: complete wound dehiscence and 8 intestinal fistulas (4 jejunal, 2 ileal and 2 fistulas of the transverse colon).*

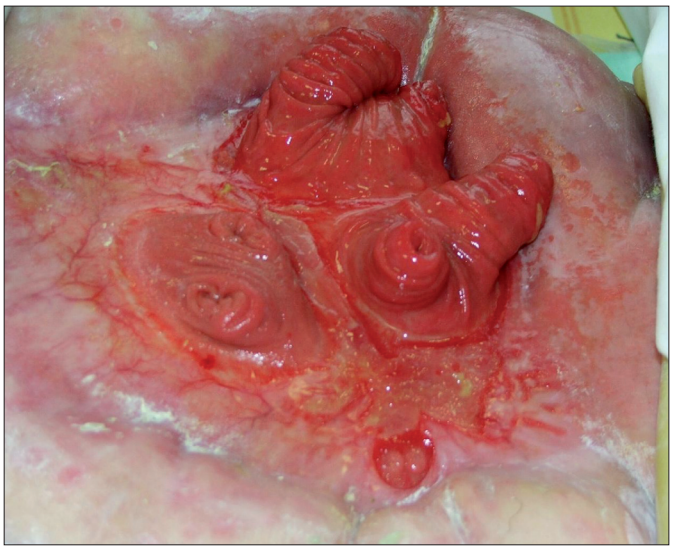

Fig. 2 - *Situation before operation after 5 months of conservative treatment (parenteral nutrition, drainage of fistulas and local administration of hyaluronan-iodine). The abdominal cavity is obliterated by apparent intestinal fistulas.*

Fig. 3 - *Situation 3 days after surgery consisting of jejunojejunal anastomosis and hemicolectomy with ileotransverse anastomosis. The open abdominal cavity was treated again with hyaluronan-iodine complex.*

Fig. 4 - *Granulation tissue covering a small part of the wound 2 weeks after operation.*

resected and bowel continuity (single or multiple anastomosis) was reconstructed successfully in all patients during this surgical procedure. In 4 subjects final closure of the abdominal cavity was possible (Tab. II). The abdominal wound could not be closed in 4 patients due to abdominal wall defects and because there was too much tension to permit fascia and skin reapproximation (Figs. 1-8). In these 4 patients, the open abdomen and intestinal loops were again covered with hyaluronan–iodine-impregnated gauze. In spite of multiple sutures no dehiscence developed in any patient. The wound healed spontaneously in 3 patients, while the granulation tissue

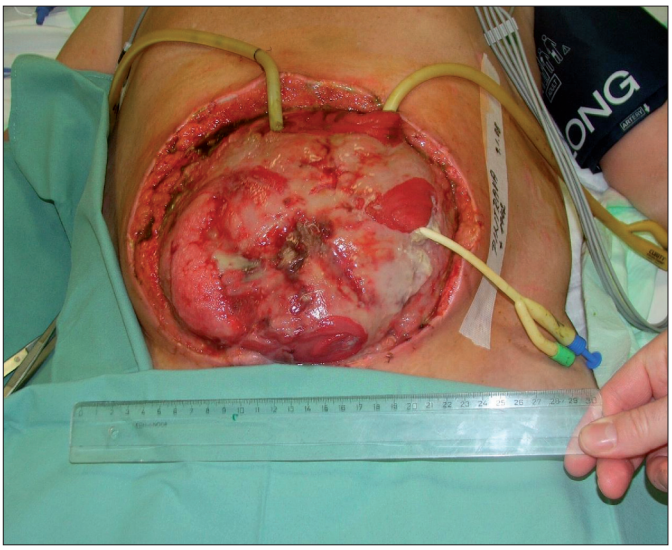

Fig. 5 - *A 69-year-old man with a large abdominal wound after complicated sigmoid cancer resection and subsequent reoperations in a local hospital. Result: complete wound dehiscence and 6 intestinal fistulas (4 jejunal and 2 fistulas of the transverse colon).*

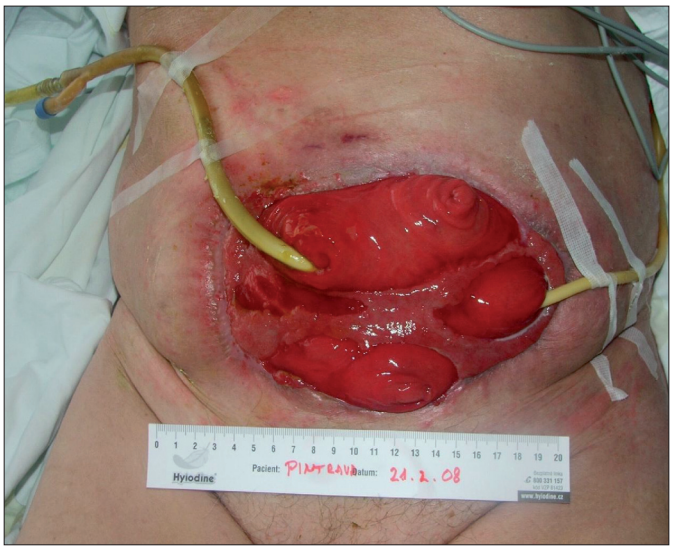

Fig. 6 - *Situation after 2 months of conservative treatment (parenteral nutrition, drainage of fistulas and local administration of hyaluronan-iodine). The abdominal cavity is obliterated by apparent intestinal fistulas*

Fig. 7 - *Situation 3 days after surgery consisting of jejunojejunal anastomosis and resection of the transverse colon with anastomosis. The open abdominal cavity was treated again with hyaluronan-iodine complex.*

Fig. 8 - *Complete wound healing 5 weeks after operation and 1 week after skin transplantation.*

on the exposed abdominal cavity was covered by skin autograft in 1 patient (Fig. 8). In spite of difficult, large and complicated abdominal wounds all patients were successfully discharged from the hospital. No adverse or allergic side effects were apparent in any patient treated with hyaluronan-iodine complex.

DISCUSSION

Abdominal wound dehiscence complicated by multiple fistulas is still associated with a high rate of complications (new fistula formation) and even mortality. Combination of severe malnutrition and abdominal sep-

sis greatly limits the spontaneous or surgically-obtained healing rate.

The results of our study imply that treatment of these patients must be complex. Careful drainage of intestinal fistulas by negative pressure is an important part of complex treatment. It reduces wound maceration but also decreases systemic inflammation. Routine use of TPN and careful monitoring of nutritional parameters is of paramount importance in these hard-to-treat complicated patients. TPN is essential for improvement of general catabolic condition, nutrition status, proteosynthesis and wound healing. It also enhances the patient's muscle function and physical activity, which is essential for the final (usually delayed) surgical procedure.

According to our results, topical treatment with a hyaluronan-iodine complex is a useful adjunct to complicated abdominal wound care. This complex improved the rate of granulation tissue formation and enhanced the rate of wound healing in comparison with our previous experience. Despite the presence of intestinal perforations and fascia necrosis, the wound condition improved and subsequent delayed surgical procedures were completed in all 7 patients. After resection of intestinal fistulas all intestinal anastomoses healed without any fistula formation including cases where abdominal closure was not possible (Fig. 1-8).

Hyaluronan is a major structural molecule in the extracellular matrix. It provides structural support for tissue regeneration and is crucial for developmental regulation, especially in the fetal period (9). In the extracellular matrix, hyaluronan creates an hydrophilic environment, regulates water retention, ionic and molecular diffusion, and forms 3-dimensional structures (7). Hyaluronan also assists in receptor-mediated gene expression (7). In children its concentration in wound fluid peaks early after injury and decreases significantly within 3 to 24 hours (10). As a major molecule, it affects inflammation regulation, regulation of oxidative stress (11), angiogenesis, granulation formation (12), and re-epithelialization; it therefore appears to be a very versatile agent. Hyaluronan may increase the rate of granulation tissue formation, decrease the formation of fibrotic tissue, and improve the rate of healing. Several studies showed that hyaluronan increases bone regeneration (13). Hyaluronate is also important for healing during the fetal period (9).

Several studies reported varying levels of success in different wound categories both in human and animal models. It was shown that sodium hyaluronate was effective in vesical mucosa healing in rabbits (14). Hyaluronan improved the healing process in injured menisci of New Zealand white rabbits up to 12 weeks after injury (15). The therapeutic effect of hyaluronic acid in mucosal wound healing was confirmed in human studies (16). In a multicenter controlled study, 50 patients with venous ulceration were treated daily with dextranomer cream or hyaluronan-impregnated gauze. Faster closure of ulceration was observed in the group treated with hyaluronan (17).

Pure hyaluronate, however, is not normally used for wound dressing. The problem is that hyaluronate can be split by hyaluronidase bacteria present on the wound surface. According to our previous results the combination of hyaluronate with iodine prevents hyaluronate splitting. The hydrophilic properties of high-molecular-weight hyaluronan attracted water from the patient's tissue, which concentrated moisture under the dressing and possibly led to the concentration of endogenous growth regulators in the wound area.

In spite of the increasing resistance to various antibiotics used to treat surgical wound infections, no significant variation in the susceptibility to iodine antiseptics was demonstrated during this 6-year study (18). Moreover, povidone-iodine dramatically increased the healing rate of chronic leg ulcers in comparison with silver sulfadiazine or chlorhexidine digluconate, although typical antimicrobial activity was similar (19). No changes in fibroblast viability, morphology, cellular proliferation, or ability to produce collagen in vitro were found in iodine concentrations of up to 0.45% in cadexomer-iodine complex (20).

We conclude that a combined approach to complicated abdominal wounds is necessary. This approach must be based on TPN, suction of intestinal secretions and local treatment. In our study the use of hyaluronan-iodine complex proved highly effective in the local treatment of complicated abdominal wounds. Our study was only an observational one and prospective studies are needed to substantiate our observations. However, as all our patients healed remarkably well, we can presume that the hyaluronan-iodine complex method is an effective method for the local dressing of difficult-to-heal abdominal wounds.

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