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ILEUS POSTOPERATOIRE

Mécanismes et Prévention

JURY

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On dit que le temps change les choses,
mais en fait il ne fait que passer et nous
devons changer les choses nous même
(Andy Warhol)

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Publications et conférences

Publications principales

- **Venara A**, Duchalais E, Dariel A, Aubert P, Durand T, Meurette G, Rolli-Derkinderen M, Hamy A, Neunlist M. Observed anti-inflammatory effects of enhanced recovery programs in early stage of colorectal surgery for cancer: from bench to bedside. 2017 (*Accepté par le World J Surg avec modifications*)
- Bougard M, Hamy A, Mucci S, Lemoult A, Parot-Schinkel E, Vielle B, Darsonval A, Neunlist M, **Venara A**. Perioperative Transcutaneous Tibial Nerve Stimulation would prevent postoperative ileus: a preliminary simple-blind randomized study 2017 (en cours de *soumission à British J surg*)
- **Venara A,** Slim K, Regimbeau JM, Ortega-Deballon P, Vielle B, Lermite E, Meurette G, Hamy A. Proposal of a new classification of postoperative ileus based on its clinical impact- results of a global survey and preliminary evaluation in colorecal surgery. Int J Colorectal Dis 2017 ;32 :797-803.
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- Barbieux J, Hamy A, Talbot MF, Casa C, Mucci S, Lermite E, **Venara A.** Does early rehabilitation reduce the time to bowel motility recovery after colorectal surgery? J Visc Surg 2017 ;154 :79-85.
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- **Venara A,** Neunlist M, Slim K, Barbieux J, Colas PA, Hamy A, Meurette G. Postoperative ileus : Pathophysiology, incidence, and prevention. J Visc Surg 2016 ; 153 :439-46.

Communications orales

- La réhabilitation améliorée peut se faire en cas de chirurgie urgente et d'occlusion colique. **Venara A**, Colas PA, Barbieux J, Philippe JB, Talbot MF, Hamy A. (*Communication orale au congrès national roumain de chirurgie, Sinaia juin 2016 et communication orale au symposium du Groupe Francophone de Réhabilitation améliorée, Paris, mai 2106*)
- La réhabilitation améliorée peut se faire en cas de chirurgie urgente et d'occlusion colique. **Venara A**, Colas PA, Barbieux J, Philippe JB, Talbot MF, Hamy A. (*Communication orale au congrès national roumain de chirurgie, Sinaia juin 2016 et communication orale au symposium du Groupe Francophone de Réhabilitation améliorée, Paris, mai 2016*)
- Quel impact à la réhabilitation améliorée sur les fistules anastomotiques après chirurgie colorectale ? **Venara A**, Barbieux J, Colas PA, Talbot MF, Lermite E, Hamy A. (*Communication orale au congrès national roumain de chirurgie, Sinaia 2016)*
- Enhanced Recovery Programs after colorectal surgery reduces postoperative ileus involving the COX pathway**. Venara A**, Duchalais E, Dariel A, Aubert P, Durand T, Meurette G, Rolli-Derkinderen M, Hamy A, Neunlist M.

(*Communication orale au congrès de l'American College of Surgeons à Washington DC, octobre 2016*).

- La glutamine pourrait prévenir l'iléus postopératoire après chirurgie colorectale. **Venara A,** Bazerie P, Barbieux J, Reynier P, Chao de la Barca J, Vielle B, Brochard C, Meurette G, Aubé C, Neunlist M, Hamy A. (*Communication au congrès de l'Association Française de Chirurgie, Paris 2016*)
- L'observance des programmes de réhabilitation améliorée diminue l'inflammation per-opératoire pendant la chirurgie colo-rectale. **Venara A**, Duchalais E, Dariel A, Aubert P, Durand T, Meurette G, Rolli-Derkinderen M, Hamy A, Neunlist M. (*Communication au congrès de l'Association Francaise de chirurgie, Paris 2017*)

Communications affichées

- Bougard M, Hamy A, Mucci S, Lemoult A, Parot-Schinkel E, Vielle B, Darsonval A, Neunlist M, **Venara A**. Perioperative Transcutaneous Tibial Nerve Stimulation would prevent postoperative ileus : a preliminary simple-blind randomized study

Abréviations

5 -HT4R :	Récepteur à la 5 hydroxytryptamine 4
AA :	Acide Arachidonique
ACh :	Acétylcholine
AE :	Analgésie Péridurale
AINS :	Anti-Inflammatoires Non Stéroïdiens
Alpha7AChR :	Récepteur à l'Acétylcholine Alpha 7
ARNm :	Acide Ribo-Nucléique messager
BEI :	Barrière Epithéliale Intestinale
CEI :	Cellules Epithéliales intestinales
COX :	Cyclo-Oxygénase
DHA :	Acide Docosahexanoïque
EPA :	Acide Eicosapentanoïque
GI :	Gastro-intestinal
GMP :	Guanylate MonoPhosphate
HPGDS :	Hematopoietic Prostaglandin D Synthase
ICAM :	InterCellular Adhesion Molecule
IC95% :	Intervalle de Confiance à 95%
IL :	Interleukine
IMC :	Indice de Masse Corporelle
iNOS :	Oxyde-nitrique synthase inductible
INF :	Interféron
IPAN :	Intrinsic primary afferent neurons
IPO :	Iléus postopératoire
JAK :	Janus Kinase
LOX :	Lipo-Oxygénase
LPGDS :	Lipocalin type Prostaglandin D Synthase
LPS :	LipoPolySaccharides
MCP-1 :	Monocyte Chemotactic Protein 1
MI :	Manipulation Intestinale
mPGES1 :	microsomal Prostaglandine E Synthase 1
NA/NC :	Non Adrénergique / Non Cholinergique
NO :	Monoxyde d'Azote
OR :	Odd Ratio
PG :	Prostaglandine
PGI2 :	Prostacycline
RA :	Réhabilitation Améliorée
SNE :	Système nerveux entérique
SNG :	Sonde Naso-Gastrique
SP :	Substance P
STAT :	Signal Transducer and activator of transcription 3
TH1 :	Lymphocytes T Helpers 1
TLR4 :	Toll Like Receptors 4
TNF :	Tumor Necrosis Factor
VIP :	Vasoactive Intestinal Peptide

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Etude Thématique

I. Introduction générale

L'iléus postopératoire est un problème de santé publique dont le coût annuel est estimé à 750 000 000 de dollars aux Etats-Unis (4,5), et ce coût est probablement proportionnellement superposable en France. En chirurgie colorectale, bien que les programmes de réhabilitation améliorée aient significativement réduit le délai de reprise du transit, et ainsi réduit l'incidence des iléus postopératoires (IPO) (6), leur incidence reste toujours importante, entre 20 et 30% en fonction des définitions. La chirurgie colorectale est souvent utilisée comme modèle d'étude des iléus car le management au sein de protocoles de réhabilitation améliorée et la faible morbidité opératoire en font un modèle relativement reproductible. Toutefois, aucune spécialité chirurgicale n'est épargnée par l'iléus postopératoire, qui peut avoir lieu même après une pose de prothèse de hanche avec 1% (7,8).

En plus d'entrainer une augmentation du coût de la prise en charge par le biais notamment d'une augmentation de la durée d'hospitalisation, l'iléus postopératoire augmente la morbidité opératoire et pourrait être lié notamment à l'apparition de fistules anastomotiques dans le cadre de la chirurgie colorectale (9). De plus, après un arrêt prolongé du transit, les patients présentent généralement des douleurs de coliques peu réceptives aux antalgiques usuels, laissant le chirurgien impuissant, et le patient inconfortable.

Son incidence et donc son coût pour la société est amené à augmenter au cours des prochaines années tant l'incidence des cancers digestifs est en constante augmentation

et tant la chirurgie abdominale, bien qu'elle ait tendance à devenir mini-invasive, augmente ses indications (notamment par le biais de la chirurgie fonctionnelle).

Des efforts de prévention de l'iléus ont été faits au cours des dernières années par le biais notamment des programmes de réhabilitation améliorée qui permet la réduction du stress chirurgical et améliore la récupération des fonctions motrices gastro-intestinales. Ces programmes intéressent toute la période périopératoire en associant des interventions nutritionnelles (hydrates de carbone préopératoires, immunonutrition préopératoire, réduction du jeûne préopératoire et réalimentation précoce postopératoire), des interventions de réduction du traumatisme chirurgical (réduction des drains, approche mini-invasive, diminution des apports intra-veineux) et la stimulation vagale par le biais de la mastication de chewing-gums.

La mastication de chewing-gums et donc la stimulation vagale ont prouvé leur efficacité sur la reprise du transit en réduisant la durée du retour à la normale et l'apparition d'un iléus. Toutefois, le côlon n'ayant pas ou que peu de terminaisons nerveuses, la stimulation vagale n'agit que sur l'intestin grêle alors que l'iléus touche la totalité du tube digestif. Il existe donc un axe d'amélioration de la prise en charge de l'iléus par le biais d'actions sur le côlon. Cependant, la littérature s'est à ce jour surtout intéressée aux mécanismes de l'IPO dans l'intestin grêle, plus que dans le côlon qui a aussi un rôle dans l'iléus et qui, par ailleurs, est le dernier organe du tube digestif à récupérer sa fonction motrice après la chirurgie.

Une meilleure connaissance de la physiopathologie de l'iléus postopératoire colique pourrait permettre de mieux appréhender de nouvelles voies de prévention ou thérapeutiques.

II. Anatomie et physiologie du tube digestif

A. Anatomie

Le tube digestif correspond aux organes creux impliqués dans la digestion du bol alimentaire. Il débute à la bouche et se termine à l'anus (figure 1). D'autres organes non creux interviennent dans la digestion. Il s'agit de glandes endocrines ou exocrines qui sécrètent des enzymes et hormones impliquées dans la digestion. Ainsi le foie intervient dans la digestion des graisses par le biais de la sécrétion de bile ou dans la digestion des sucres, de même que le pancréas qui intervient dans la digestion des graisses par le biais de la sécrétion des sucs pancréatiques. La vésicule biliaire ne secrète pas directement d'enzyme mais est le réservoir de la bile et permet le largage d'une grande quantité de bile lors de l'arrivée du bol alimentaire dans le duodénum.

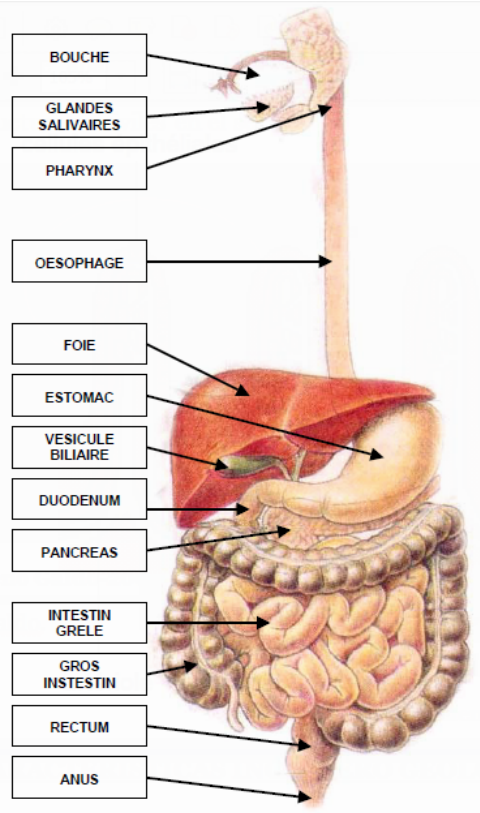


Figure 1 : Représentation du tractus digestif – *Source* http://www.monografias.com/trabajos95/digestion/image006.png ®

B. Histologie

La bouche et l'œsophage sont des organes de transformation (bouche) et de transit (œsophage). Aucune implication de ces organes dans la physiopathologie de l'iléus postopératoire n'est rapportée dans littérature et ils ne seront pas décrits dans le chapitre suivant.

1. L'estomac

L'estomac est l'organe creux où se poursuit la digestion initiée dans la bouche lors de la mastication et du mélange avec les enzymes salivaires.

Sur le plan histologique, il comporte quatre couches :

- *L'épithélium*:

Il s'agit d'un épithélium cylindrique avec des cryptes variable selon la localisation.

  - Au niveau du Cardia, on retrouve les cellules à pôle muqueux fermé et des cellules à mucus (glandes cardiales).
  - Au niveau du fundus, on retrouve les cellules principales (pepsines), des cellules à pôle muqueux fermé, des cellules bordantes (HCl, facteur intrinsèque), et des cellules neuroendocrines (histamine, sérotonine, gastrine…). Les cellules neuroendocrines expriment des marqueurs nerveux (CD-56, N-CAM…)
  - Au niveau de l'antre, on retrouve les cellules à pôle muqueux fermé, des cellules muco-secrétantes et des cellules neuroendocrines (gastrine…).

- *La sous muqueuse*

Elle contient un tissu conjonctif riche en vaisseaux et en tissu nerveux.

- *La musculeuse*

A la différence des autres organes creux, elle se compose en 3 couches de cellules musculaires lisses (longitudinales, circulaires et obliques).

- *La séreuse*

2. L'intestin grêle

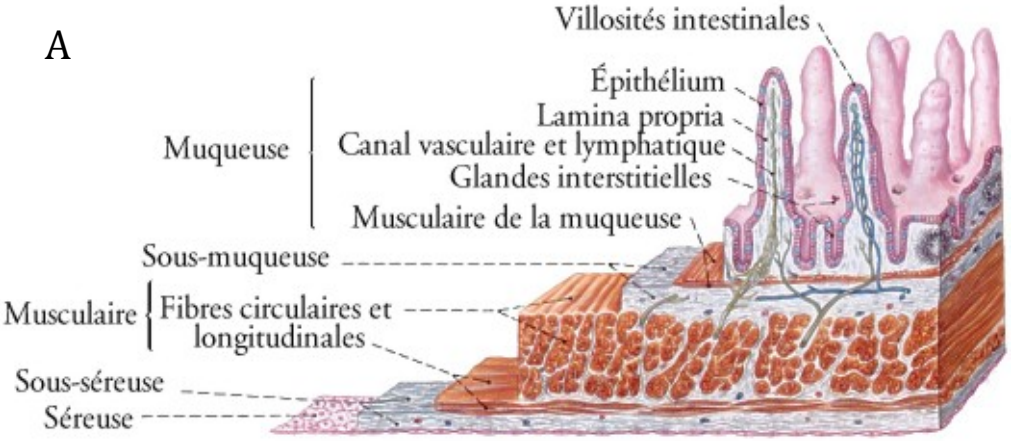
L'intestin grêle se divise en 3 segments : le duodénum, le jéjunum et l'iléon. Il mesure environ 5 mètres et sa surface est multipliée grâce à 3 niveaux de replis : les valvules conniventes, les villosités, les microvillosités. Ainsi la surface d'absorption avoisine les 40-50 m^2. Comme l'estomac, il se compose en 4 couches :

- *L'épithélium*

Il est composé d'une seule couche avec 5 types de cellules : les entérocytes, les cellules de Paneth (défense contre les bactéries par la secrétion de lysozymes et défensine), les cellules calciformes (mucus), les cellules argentaffines, les cellules absorbantes.

L'épithélium repose sur une fine membrane basale. Le tissu conjonctif forme l'axe des villosités et le chorion comporte les nodules lymphoïdes ainsi que la trame réticulaire avec les plasmocytes et des lymphocytes. L'axe des villosités est occupé par les vaisseaux et les lymphatiques (figure 2).

A



B

Figure 2 : (A) coupe de la paroi de l'intestin grêle et (B) vue en coupe de l'intestin grêle source : http://www.corpshumain.ca/Intestin.php# ®

- *La sous-muqueuse*

Il contient les vaisseaux sanguins et lymphatiques, ainsi que le plexus nerveux de Meissner. Le plexus de Meissner intervient plutôt dans la sécrétion gastro-intestinale ou dans le contrôle du débit sanguin local.

- *La musculeuse*

Elle contient 2 couches de cellules musculaires lisses (circulaire interne et longitudinale externe). Entre les 2 couches musculaires, on trouve les cellules de Cajal et le plexus nerveux myentérique d'Auerbach.

- *La séreuse*

Elle correspond au péritoine viscéral.

Au niveau de l'iléon, il existe des plaques de Peyer au niveau du chorion de la muqueuse. Ces plaques de Peyer sont des follicules lymphoïdes isolés. Elles sont composées essentiellement de cellules lymphoïdes B et T qui sont séparées de la lumière intestinale par les cellules M.

3. Le côlon

Faisant suite à l'intestin grêle après le passage par la valvule iléo-caecale (dite de Bauhin), le côlon se divise en plusieurs segments : le caecum, l'appendice, le côlon ascendant, le côlon transverse, le côlon descendant, le côlon sigmoïde, le rectum et le canal anal. La valvule de Bauhin est un repli muqueux situé au niveau d'un repli de la face interne du caecum.

La structure histologique est semblable à celle de l'intestin grêle mais la muqueuse est épaisse et comporte de nombreuses cellules à mucus (figure 3). De même, la musculeuse est composée des deux couches (circulaire interne et longitudinale externe) mais la longitudinale externe est discontinue (interrompue au niveau des bandelettes).

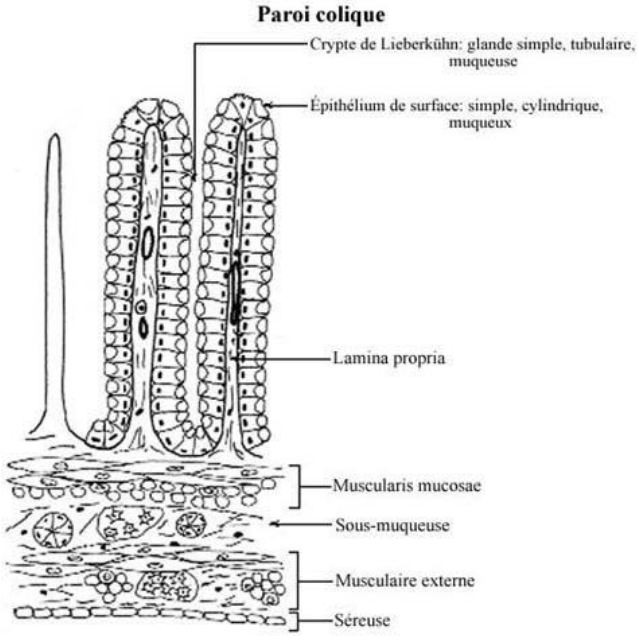


Figure 3 : Coupe histologique de la paroi du côlon

source : http://mapageweb.umontreal.ca/cabanat/bio2412/Chapitre13.html#côlon ®

C. Physiologie

1. L'estomac

L'estomac sécrète environ 1500 mL de liquide digestif par jour. Le liquide digestif se compose essentiellement l'acide gastrique, de la pepsine, de la lipase gastrique, du facteur intrinsèque et du mucus.

L'innervation sympathique est inhibitrice de la motricité intestinale et est stimulée par le stress. L'innervation parasympathique (vagale) est activatrice de la motricité et est stimulée par la vue, l'odeur (reflexe de Pavlov), la mastication...

2. L'intestin grêle

Le duodénum est la zone où le chyme est digéré par les sucs pancréatiques (1500 à 2000 mL par jour) et la bile (800 à 1000 mL par jour) (lipides). Ces sucs sont libérés au niveau de l'ampoule de Vather après avoir été synthétisés respectivement par le pancréas et le foie. Le sphincter d'Oddi se relâche au moment où le chyme arrive après être passé et avoir été transformé dans l'estomac.

Par ailleurs, le jéjunum et l'iléon sécrètent environ 2000 mL de liquides par jour. L'intestin grêle est une zone d'absorption. L'absorption est différente suivant que le chyme se trouve dans le jéjunum ou dans l'iléon.

Ses fonctions sont multiples : brassage, absorption, endocrine et immunitaire.

3. Le côlon

Le rôle du côlon est essentiellement un rôle moteur et un rôle de réabsorption d'eau et d'électrolytes. Le rectum a plutôt un rôle de réservoir et de réflexe à la défécation.

D. Système nerveux autonome

Le système nerveux autonome digestif se compose de trois systèmes : le système parasympathique, le système sympathique et le système nerveux entérique.

Le système nerveux autonome parasympathique excitateur de la motricité gastro-intestinale est composé du nerf vague et des nerfs pelviens au niveau du côlon. La densité des nerfs vagaux diminue sur un axe rostro-caudal pour devenir quasi-inexistant au niveau colique ou rectal (10). Le principal neuromédiateur est la l'acétylcholine.

Le système nerveux autonome sympathique est inhibiteur de la motricité. Il provient des ganglions coeliaques et mésentériques. Le neuromédiateur des neurones post ganglionnaires est la noradrénaline et inhibe le système nerveux entérique ou encore agit directement sur les muscles sphinctériens en induisant leur contraction.

Le système nerveux entérique (SNE) est composé des plexus sous muqueux (de Meissner) et des plexus myentériques (d'Auerbach) (figure 4). Ils sont organisés en structure ganglionnaire présents tout le long du tube digestif de l'oesophage (1/3 inf) au rectum. Les ganglions du SNE sont composés de neurones, cellules gliales entériques et cellules souches neurales.

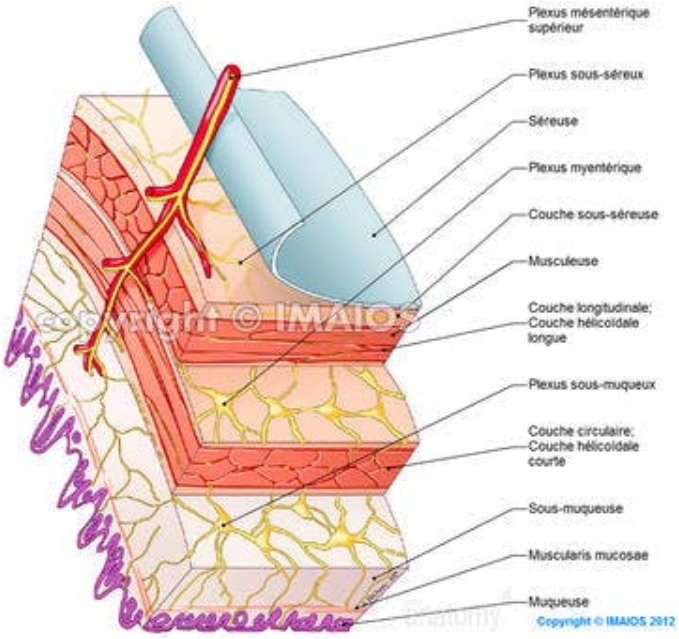


Figure 4 : Représentation de la localisation des plexus nerveux du SNE.

Source : https://www.imaios.com/fr/e-Anatomy/Thorax-Abdomen-Pelvis/Systeme-digestif-Illustrations ®

Les fibres nerveuses présentes au sein des plexus ont deux origines :

- extrinsèque (les corps des neurones sont en dehors du SNE) que sont les axones postganglionnaires sympathiques et les axones préganglionnaires parasympathiques
- intrinsèque

Les neurones entériques peuvent être classés selon leur fonction (sensorielle, montoneurone ou interneurone).

Ainsi, les neurones sensitifs présents dans les plexus sont en communication avec un interneurone. L'interneurone va ensuite envoyer l'information vers le motoneurone situé dans le muscle, dans l'épithélium ou dans l'endothélium.

Ces neurones polarisés contiennent des combinaisons de neuromédiateurs spécifiques en fonction de la polarisation, ce qui conduira à des effets fonctionnels différents en fonction des récepteurs présents sur les cellules cibles et qui permettra une activité coordonnée (sécrétion, motricité).

E. Motricité

1. Temps de transit normal

La durée du transit normal est variable selon les individus (11) est mesurée en moyenne à 56 heures (12). Le temps de transit gastrique est d'environ 2 heures, de l'intestin grêle 4-5 heures et du côlon entre 40 et 70 heures (11).

Elle varie selon certains facteurs non modifiables, tels que l'âge avancé qui ralentit spécifiquement le transit colique par rapport à un individu plus jeune ou modifiables tels que le tabac qui accélère le transit global (30 heures vs 59 heures, p=0.002) (11). Par ailleurs, l'indice de masse corporelle (IMC) ou le sexe ne modifieraient pas la durée du transit (11) bien que le sexe féminin pourrait augmenter le temps de transit colique (13).

2. Péristaltisme

Les cellules musculaires lisses ont une activité électrique de base. Elles se dépolarisent régulièrement sous l'influence des cellules interstitielles de Cajal situées dans les différentes couches musculaires et connectées aux cellules lisses par des jonctions communicantes. Ces ondes de dépolarisation ont une fréquence plus élevée dans l'intestin grêle que dans le côlon. Leur potentiel de repos est d'environ -50 mV et les dépolarisations régulières forment le rythme électrique de base. Ces dépolarisations n'entrainent pas de contraction musculaire. Il faut attendre l'apparition d'une activité neuronale pour déclencher une contraction et sa propagation directionnelle.

La succession coordonnée des contractions musculaires qui permettent l'avancée du bol alimentaire dans la lumière digestive définit le péristaltisme. Ces contractions musculaires sont une réponse à un stimulus local mécanique ou chimique, ou à une distension du tube digestif et sont régulées par le SNE.

Le plexus d'Auerbach coordonne les deux couches musculaires et après application d'un stimulus local, les mécanorécepteurs vont stimuler l'interneurone qui va envoyer une information vers le motoneurone d'amont libérant des neuromédiateurs ayant des effets de contraction sur les muscles lisses circulaires (ACh, SP), et vers le motoneurone d'aval libérant des neuromédiateurs ayant des effets de relaxation de la circulaire interne (NO, VIP…) (figure 5). Cette onde péristaltique va se propager par stimulation locale de contiguïté (14).

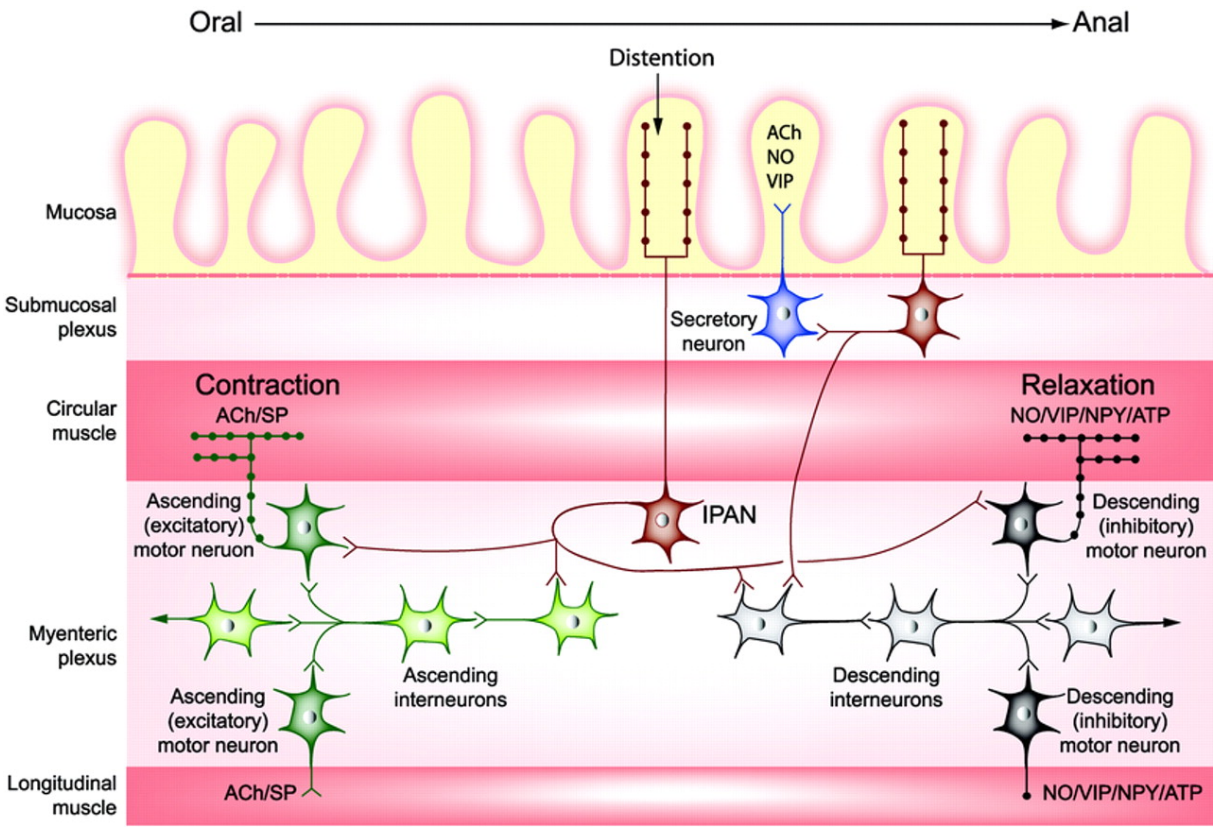


Figure 5 : Physiologie du péristaltisme. Source : Benarrocch EE (1)

La contraction n'est pas la même au niveau du côlon et au niveau de l'intestin grêle puisque la contraction est plutôt circulaire au niveau de l'intestin grêle (propagation de l'onde synchrone) alors qu'elle est plutôt vermiculaire au niveau du côlon (propagation de l'onde asynchrone).

F. Barrière Epithéliale Intestinale (BEI)

1. Généralités sur la BEI

La BEI sépare la paroi intestinale de sa lumière. Elle prévient le passage des bactéries intra-luminales tout en laissant passer les nutriments alimentaires nécessaires à notre survie.

Il existe quatre niveaux de barrière :

- Le microbiote intestinal.
- L'épithélium intestinal qui est formé d'une monocouche de cellules épithéliales intestinales (CEI) liées par des jonctions intercellulaires qui contrôlent le passage de molécules entre les cellules.
- Le mucus qui est constitué de mucine. Ce mucus contient des agents antibactériens tels que les défensines sécrétées par les cellules de Paneth. Par ailleurs, les charges négatives des mucines créent une barrière de diffusion sélective pour le passage des petites molécules ioniques.
- Le système immunitaire qui tolère les bactéries commensales et les antigènes alimentaires. Les principaux types cellulaires sont les macrophages, les granulocytes, les cellules dendritiques (cellules phagocytaires), des cellules NK et des mastocytes situés dans la *lamina propria*.

2. BEI en rapport avec l'épithélium intestinal

L'épithélium intestinal constitue une barrière physique par l'intermédiaire d'interactions entre cellules (cellule-cellule) ou avec la matrice (cellule-matrice).

a) Interactions cellule-cellule

L'espace entre les deux cellules est scellé par des jonctions intercellulaires assurant une véritable frontière entre les deux milieux. Ces jonctions sont localisées au niveau apical et latéral des CEI. Les complexes jonctionnels regroupent les jonctions serrées, les jonctions adhérentes, les desmosomes et les jonctions communicantes (15).

Les jonctions serrées (*zonula occludens*), sont situées au niveau du pôle apical des CEI et sont formées par des protéines transmembranaires de la famille des claudines, occludines, Junctional adhesion molecules et tricellulines

Les jonctions adhérentes (*zonula adherens*) relient les CEI via des interactions Calcium dependantes (avec la protéine transmembranaire cadhérine E)

Les desomosomes (*macula adherens*) relient les CEI par des filaments intermédiaires de cytokératine.

Les jonctions communicantes (macula occludens) qui relient le cytoplasme des CEI entre eux par des canaux intercellulaires. L'ouverture des canaux dépend de la phosphorylation des connexines, protéines transmembranaires qui la composent (16).

b) Interactions cellule-matrice

Les CEI reposent sur une matrice extra-cellulaire, la lame basale, à laquelle elles sont reliées à leur pôle baso-latéral par les hémidesmosomes et par les adhésions focales.

3. Perméabilité de la BEI

La perméabilité intestinale permet le passage des nutriments nécessaires à la vie dans la circulation sanguine. Elle peut être mesurée ex-vivo ou in-vivo chez l'Homme ou l'animal.

Afin de l'évaluer, plusieurs techniques similaires ont été décrites. Elles reposent sur la mesure du passage de différents éléments dosables et non métabolisables (sucres) pour évaluer leur capacité à traverser la BEI et entrer dans le réseau vasculaire (*in vivo*) ou dans le pôle basolatéral (fluorescence en chambre de Ussing, *ex-vivo*) (17).

L'absorption peut se faire par **une voie transcellulaire** qui est un transport passif ou actif de molécules à travers les membranes plasmiques apicales et basolatérales des CEI et **une voie paracellulaire** qui permet le passage des ions et des molécules hydrophiles inférieures à 600 Da.

Le transport paracellulaire est essentiellement régulé par les jonctions serrées (18). Le passage paracellulaire n'est pas qu'un phénomène passif. La diffusion est aussi limitée par la sélectivité de taille et de charge des jonctions serrées (19).

Concernant le transport transcellulaire, il existe un passage passif qui s'effectue selon le gradient de concentration et ne nécessite pas de consommation d'énergie. Le transport actif s'effectue contre le gradient de pression et nécessite la consommation d'une molécule d'ATP ou un gradient électrochimique d'une autre molécule. Ce transport actif nécessite soit un transporteur, soit des phénomènes d'endocytose ou d'exocytose (macromolécules) (19,20).

Le passage des bactéries et agents pathogènes peut se faire par le biais de la perméabilité paracellulaire (ouverture des jonctions serrées) ou par le biais de la perméabilité transcellulaire (transcytose) (21).

III. Notions préliminaires

La partie « généralités » a fait l'objet d'une publication dans le Journal de Chirurgie Viscérale en 2016. Le chapitre suivant est donc en grande partie inspiré de cet article (22).

A. Définitions

1. Iléus Postopératoire

L'iléus postopératoire est défini comme un ralentissement ou un arrêt du transit secondaire à la chirurgie (23) quel qu'en soit l'abord ou la spécialité. Si la définition du concept de l'iléus est relativement consensuelle, sa durée normale est quant à elle laissée à l'appréciation des auteurs. Cette absence de consensus était déjà rapportée en 2005 mais reste, à ce jour, toujours d'actualité (24).

En 1990, une étude physiopathologique rapportait que la récupération du transit gastrique intervenait après 24-48 heures, celle de l'intestin grêle dans les 12-24 heures alors que celle du côlon intervenait dans les 3 à 5 jours (25).

La physiopathologie ne permet pas de définir de manière fiable la durée normale de reprise du transit mais Vather *et al.* (26) ont proposé en 2013 une définition basée sur une revue de la littérature et sur un sondage auprès d'experts. Cette définition ne répond toutefois qu'à des critères cliniques mais n'a pas uniformisé la durée normale de l'iléus. Ainsi, l'iléus postopératoire se définit par la présence d'au moins 2 des 5 facteurs suivants :

- nausées/ Vomissements ≥ 2 reprises

- impossibilité à tolérer l'alimentation orale solide ou semi-solide au cours de 2 repas consécutifs
- distension abdominale
- absence de gaz et/ou selles durant 24 heures consécutives
- imagerie réalisée dans les 24 heures précédant le diagnostic, en faveur d'un iléus postopératoire.

A cette définition, les auteurs ajoutaient la notion d'iléus prolongé si il durait au moins 4 jours (26). Cette notion n'a cependant pas été retenue par la communauté puisqu'on retrouve dans la littérature des durées très variables (22). Selon les auteurs, la limite retenue variait entre 1 et 8 jours (26–34).

2. Iléus postopératoire secondaire

Ainsi, l'iléus postopératoire peut avoir plusieurs qualificatifs dans la littérature. Les auteurs le qualifient de primitif lorsqu'il est uniquement lié à l'acte chirurgical et de prolongé ou de pathologique lorsqu'il dure plus longtemps que la durée normale supposée. D'autres auteurs ont ajouté la notion d'iléus secondaire qui n'a plus la même physiopathologie que l'iléus postopératoire. En effet, l'iléus est qualifié de secondaire lorsqu'il fait suite à une fistule, une péritonite ou à un abcès intrapéritonéal (4). Dans ce cas, une cause est retrouvée et l'iléus est lié à l'infection.

Toutefois, cette définition d'iléus secondaire est actuellement discutée car un lien entre la physiologie de l'iléus et la physiologie de la fistule anastomotique a été clairement établi (35). Ainsi, la fistule anastomotique augmenterait le risque d'iléus (ou l'inverse) avec un Odd Ratio (OR) à 12 (35).

3. Critère de jugement

Le critère de jugement retenu pour évaluer la reprise de la motricité gastro-intestinale est l'association de la présence de selles et de la tolérance à l'alimentation solide (36). Il s'agit du critère de jugement le mieux corrélé à la reprise du transit.

4. Incidence des iléus postopératoires

L'incidence des iléus postopératoire telle que rapportée dans la littérature n'est pas comparable selon les auteurs puisque la définition et surtout le cut-off n'est pas le même. Ainsi, nous avons récemment rapporté une variation de l'incidence des iléus entre 2 et 60% selon la définition (de 1 à 7 jours) (6).

Toutefois, la littérature rapporte une incidence entre 3 et 32% des cas (26–28,30–32,37) en fonction du type de chirurgie, de la définition et du mode de prise en charge. En effet, la réhabilitation améliorée permet une diminution de l'incidence des iléus postopératoire corrélée à l'observance du protocole de réhabilitation améliorée (6).

Dans le cas de la chirurgie orthopédique, l'incidence des iléus n'est pas nulle et est estimée entre 0,32 et 1,6% des patients après chirurgie (7,8).

5. Classification des iléus postopératoires primitifs

La définition clinique de l'iléus postopératoire a un intérêt clinique certain puisqu'elle permet de faire le diagnostic de l'iléus et surtout elle permet de décider la prise en charge de l'iléus postopératoire en pratique clinique.

Toutefois, cette définition n'a qu'un intérêt limité dans la recherche clinique puisque la limite n'est pas consensuelle. Ainsi, l'étude des facteurs de risque et de l'incidence des iléus n'est probablement pas reproductible et comparable selon les auteurs.

Afin de pallier à ce manque de reproductibilité, nous avons proposé une classification basée non plus sur la durée mais sur les conséquences de l'iléus (Résultats 3).

Nous retenions ainsi la définition de Vather et al. de l'iléus (26) dès le jour opératoire. Ainsi, un patient n'ayant pas de gaz et un météorisme abdominal à J2 est considéré comme en iléus. La classification était quant à elle calquée sur la classification de Dindo-Clavien de la morbidité opératoire (38). Les iléus étaient donc classés sur une échelle de 5 niveau (39).

Classe A : pas de conséquence en dehors d'une augmentation de la durée d'hospitalisation

Classe B : recours à des traitements symptomatiques ou à des examens diagnostiques (arrêt ou réduction de l'alimentation, laxatifs, drogues prokinétiques, drogues antispasmodiques, drogues antiémétiques, recours à une perfusion ou augmentation de l'hydratation parentérale…)

Classe C : recours à un sondage naso-gastrique ou réhospitalisation (en cas de sortie antérieure)

Classe D : conséquences sévères de l'iléus

Grade D1 : complication générale (perturbations hydro-électrolytiques, pneumopathies, fibrillation auriculaire…)

Grade D2 : nécessité de soins intensifs ou de reprise chirurgicale

Classe E : Décès lié à l'iléus.

B. Conséquences de l'iléus

Les conséquences de l'iléus sont financières, notamment parce qu'il augmente le risque d'hospitalisation prolongée avec un Odd Ratio (OR) de 8,79 (40). Le coût de l'iléus en France n'est pas rapporté mais il est estimé à environ 750 millions de dollars/an aux Etats-Unis (4,5,25), ce qui en fait un véritable problème de santé publique.

Par ailleurs, il augmente la morbidité puisqu'il entraine une stase des secrétions gastro-intestinales avec un risque de nausées et vomissements pouvant se compliquer d'une inhalation et d'un décès. En dehors de cette complication, il peut entrainer une déshydratation, un déséquilibre hydroélecrolytique ou un sepsis.

C. Prise en charge de l'iléus

A la lumière de la physiologie, on peut comprendre que la seule mise à jeun des patients ne suffit que rarement à permettre de passer l'épisode aigu de l'iléus. En effet, lors d'un iléus paralytique complet, les fonctions sécrétrices du tube digestif ne sont pas altérées et plus de 5000 mL sont ainsi sécrétées de manière spontanée sans que le liquide ne soit évacué, menant inexorablement à des vomissements incoercibles.

Le traitement de l'iléus est à ce jour symptomatique, et il est recommandé la mise en place, en plus du jeûne, d'une sonde nasogastrique. Par ailleurs, une correction des troubles hydro-électrolytique est la règle car les patients sont souvent déshydratés en raison du 3ème secteur qui se forme lors de l'épisode aigu.

Enfin, en cas de doute sur la présence d'un iléus secondaire (en lien avec une fistule anastomotique ou un événement extérieur), un scanner abdomino-pelvien doit être demandé.

Il n’existe pas de traitement prokinétique qui ait prouvé une efficacité dans le traitement des iléus postopératoire.

IV. Facteurs de risque d'iléus postopératoire

Malgré une reproductibilité limitée par l'absence de consensus dans le cut-off définissant l'iléus prolongé ou pathologique, certains facteurs de risque ont pu être identifiés et sont régulièrement retrouvés dans les différentes études. Certains sont modifiables, d'autres sont non modifiables.

A. Facteurs de risque modifiables

La voie d'abord est également un facteur de risque d'iléus. Ainsi la laparotomie augmente le risque d'iléus alors que la coelioscopie et même la coelioscopie « hand-assisted » sont plutôt des facteurs de prévention de l'iléus posotpératoire (41).

Dans une étude rétrospective de grande ampleur, le tabac, la voie d'abord par laparotomie, la durée opératoire, la nécessité d'une chimiothérapie, l'absence de préparation intestinale orale, l'indication opératoire et l'absence d'antibiothérapie orale étaient des facteurs de risque d'iléus opératoire (42).

Parmi les facteurs de risque modifiables d'iléus postopératoire, dans le contexte d'une chirurgie non abdominale, un remplissage > 2L a été montré comme étant un facteur de risque (43). L'antibiothérapie orale associée ou non à la préparation colique pourrait prévenir l'apparition de l'iléus postopéatoire (44). Toutefois, cette donnée est nouvelle et nécessite la réalisation d'une étude prospective randomisée.

B. Facteurs de risque non modifiables

Les facteurs de risque les plus marqués retrouvés dans la littérature sont le sexe masculin, un âge avancé ou d'importantes pertes sanguines (26,27,29–32).

Le côté de résection est rapporté comme étant un facteur de risque d'iléus. Ainsi la colectomie droite, bien que réalisée par coelioscopie, est plus à risque d'iléus que la colectomie gauche (45)(46).

Une récente étude rapporte qu'un index de Charlson élevé (Tableau 1), ajusté sur l'âge, est un facteur de risque d'iléus postopératoire (47).

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Tableau 1 : Index de Charlson (3)

Dans une étude rétrospective de grande ampleur, l'âge, le sexe masculin, le type asiatique, la présence d'ascite, le surpoids et l'obésité étaient des facteurs de risque d'iléus postopératoire (42).

V. Physiopathologie des iléus postopératoires

A. Modèle animal

L'IPO résulte d'un enchainement et d'une association de processus tels que le stress opératoire, l'induction anesthésique, l'incision, la manipulation intestinale…L'étude de ces différents mécanismes a essentiellement été réalisée sur des modèles animaux (rat, souris, cochon, chien…) mais ne sont probablement que partiellement transposables à l'Homme (48). En effet, des différences de mécanismes de l'iléus ont été mises en évidence entre différentes espèces telles que le rat et la souris) (48).

Le modèle animal d'iléus a été développé initialement pour étudier l'effet de la manipulation intestinale (MI) sur la reprise du transit. La première description de ce modèle avec MI a été rapportée par Kalff *et al.* en 1998 (49). Plus récemment, Gomez-Pinilla *et al.* ont décrit un modèle de MI et d'iléus en laparoscopie (50). Le principe est similaire quelle que soit la voie d'abord. Les souris sont anesthésiées puis la chirurgie est initiée. Après une laparotomie ou sous laparoscopie, le tube digestif (en excluant le duodénum et le côlon) est palpé à l'aide d'un coton-tige ou équivalent pendant une durée d'environ 5 à 10 minutes selon les équipes. La souris est ensuite réveillée sur un tapis chauffant à 37°C.

La pression exercée sur l'intestin est importante et est source de biais puisque plus la pression augmente et plus la reprise du transit est ralentie (51). Il a été montré que le niveau d'inflammation intestinale, reflétée par IL-6, IL-1beta et MCP-1, augmentait avec la pression (51). Les auteurs recommandaient donc l'exercice d'une pression de 9 grammes sur l'intestin afin de limiter la variation intra-individuelle (51).

B. Cinétique de l'iléus postopératoire

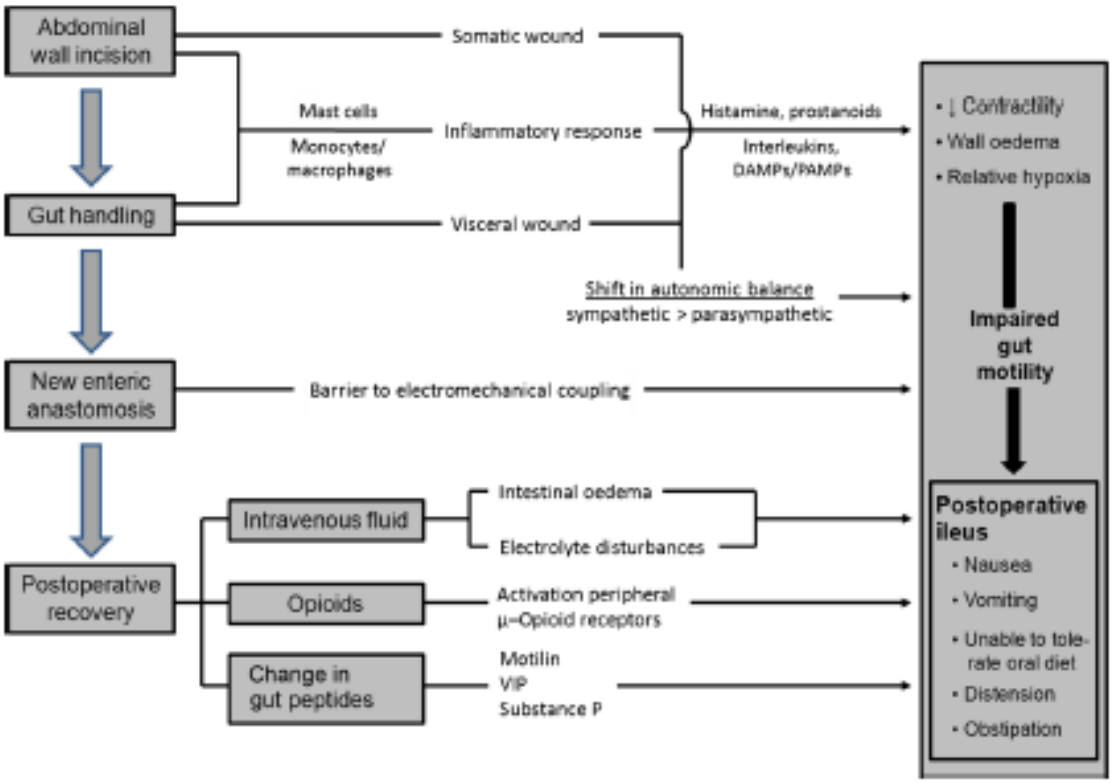


Figure 6 : Cinétique de l'iléus postopératoire

Source : Vather et al. (2).

L'iléus postopératoire est multifactoriel. Afin de simplifier la présentation de sa physiopathologie les auteurs le décrivent classiquement en 3 phases. La première phase correspond à l'implication du système nerveux (52). La seconde implique la manipulation intestinale et est médiée par l'inflammation locale. Enfin, la 3ème phase est celle de résolution qui implique une activation du système vagal. Ces trois phases sont cependant superposées et tous les modes d'action peuvent agir conjointement à un temps donné de l'histoire naturelle de l'IPO.

Nous avons donc choisi de décrire le mécanisme impliqué et non une phase à un temps donné.

1. Mécanisme neurologique

La première phase débute lors de l'anesthésie et de l'incision opératoire (53).

L'hypothalamus et le noyau du tractus solitaire inhibent la motricité intestinale après avoir été stimulés par les neurones afférents (2) devant les stimuli nociceptifs. Ils activent les efférences sympathiques pour donner le réflexe adrénergique en réponse aux stimuli nociceptifs. La libération de catécholamines dans le tube mène à l'activation des récepteurs alpha-2 adrénergiques qui inhibent au niveau présynaptique les nerfs parasympathiques cholinergique, et qui sécrètent du NO directement au niveau des muscles. L'inhibition du système vagal apparaît environ 9 heures après le début de l'intervention (54,55) et le degré de paralysie de la stimulation cholinergique sont directement liés au degré du traumatisme, de l'activation des phagocytes de la muscularis propria du tube digestif et de l'extension des cellules inflammatoires (56).

Par ailleurs, le NO est le médiateur des nerfs non-adrénergiques/non-cholinergiques (NA/NC) (57). Cette voie NA/NC entraine une sécrétion de la VIP qui inhibe la motricité intestinale. Le VIP mène à une réduction dose-dépendante de la motricité intestinale (58). Son effet est biphasique. Il réduit le potentiel membranaire excitateur de la contractilité intestinal à 12 heures puis l'augmente 3 jours après l'intervention (53).

2. Manipulation intestinale

C'est la phase la plus étudiée sur le plan physiopathologique et sur le plan thérapeutique car elle implique la manipulation intestinale.

Elle entraine une infiltration leucocytaire d'apparition progressive dans la *muscularis propria* à partir de la 3ème heure après le début de l'intervention. Les phénomènes menant à l'inflammation intestinale impliquent les macrophages, les monocytes et les mastocytes qui secrètent diverses molécules inflammatoires ou hormones qui mènent à l'IPO et qui régulent les cellules inflammatoires.

L'inflammation est liée à la manipulation intestinale. Cette inflammation est proportionnelle à l'intensité de la compression intestinale car la manipulation intestinale per-coelioscopique n'induit pas d'inflammation (58,59).

Dans un premier temps, la manipulation intestinale induit une dégranulation des mastocytes (60).

a) Dégranulation mastocytaire et recrutement cellulaire

La dégranulation des mastocytes développe l'infiltration leucocytaire dans la paroi du tube digestif (9)(61) et contribue donc au recrutement des autres cellules telles que les lymphocytes TH1 et les macrophages, résultant ainsi en une activation des macrophages résidents (49,62). Cette activation est aussi liée à une activation des cellules dentritiques qui produisent de l'interleukine (IL)-12, qui a des adhésions avec les lymphocytes

mémoires (TH1) qui migrent dans les zones non manipulées (63). Cela contribue à « l'effet champs » qui est médié par les vaisseaux lymphatiques et les organes lymphoïdes (63). Les cellules TH1 sécrètent de l'interféron (INF) alpha et active les macrophages de la *muscularis propria* (63). C'est par le biais de cet effet champs que l'iléus se propage à la totalité du tube digestif.

L'infiltration par les neutrophiles de la *muscularis propria* a été montrée comme la cause d'une dysfonction motrice gastro-intestinale par le biais de la sécrétion d'oxyde nitrique (NO) (64) ou par l'activation du réflexe neural sympathique inhibiteur (65).

Le recrutement cellulaire va s'auto-entraîner par le biais des molécules de liaisons entre cellules exprimées par les leucocytes. Ainsi, le nombre des ICAM1 et MCP1 augmente dès 3 heures après le début de la laparotomie avant de diminuer progressivement (66)(58) et ICAM1 et son ligand l'intégrine B2 médient le recrutement des cellules inflammatoires (67). ICAM1 est exprimé sur les cellules endothéliales, épithéliales, les fibroblastes et les leucocytes (67).

En effet, c'est à l'aide des ICAM, TRL4 et INF alpha que le nombre de mastocytes, macrophages et monocytes augmente dans la *muscularis mucosae* (67). Ces cellules sécrètent les interleukines (IL) 6, 8, 1 *alpha* et *beta*, l'histamine et la TNF *apha*. Ces molécules sont impliquées dans l'iléus postopératoire (63,68,69). Les interleukines augment la synthèse des molécules d'adhésion et favorisent le recrutement des leucocytes (70).

En plus d'entrainer une infiltration de la paroi du tube digestif, la dégranulation des mastocytes entraine également une accentuation de l'hyperperméabilité de la BEI déjà

initiée lors de l'anesthésie (71,72). Cette dysfonction de la barrière épithéliale intestinale caractérisée par une augmentation sa perméabilité est impliquée dans l'IPO (73).

b) Augmentation de la perméabilité membranaire intestinale

La manipulation intestinale augmente la perméabilité de la BEI qui contribue à l'iléus (74)(75). Cette hyperperméabilité pourrait résulter de l'activation des mastocytes (61)(73) bien que certains auteurs le réfutent (76). Elle favorise le passage de lipopolysaccharides (LPS) bactériens intraluminaux vers la paroi intestinale (75). Ainsi, les produits des bactéries endogènes agissent de manière synergique avec la réponse inflammatoire dans la *muscularis propria* post-chirurgicale. En effet, en transférant des LPS intracoliques, ainsi que des microsphères au sein de la *muscularis propria* intestinale, la manipulation résulte ainsi en une augmentation de l'inflammation, en stimulant le recrutement de macrophages (58). Ceux-ci se lient par le biais des Toll Like Receptors 4 (TLR4) aux liposaccharides bactériens (77). Les macrophages ont une action précoce dans le phénomène de l'iléus dès 60 min (78) et leur activation des macrophages mène à une secrétion de cytokine et chémokines 3-4 heures après le début de la manipulation (67). La concentration locale en IL1 et IL6 est maximale 3 h après le début de la manipulation (78).

D'un point de vue thérapeutique, la décontamination intestinale par une antibithérapie, ainsi que l'inhibition de TRL4 diminuent l'inflammation au sein de la *muscularis propria* (79).

c) Persistance de phénomènes nerveux via la sécrétion de NO

Trois heures après le début de la manipulation intestinale, on observe une augmentation de l'ARNm de iNOS (66). Son augmentation est rapide mais sa diminution l'est tout autant puisqu'on observe une nette décroissance de iNOS au sein de la muscularis propria colique après 6 heures. iNOS est exprimé dans les leucocytes au sein de la muscularis propria intestinale et joue un rôle majeur dans la médiation des dysfonctions du muscle lisse (58,64).

d) Activation de la chaîne de dégradation de l'acide arachidonique

Les premiers médiateurs inflammatoires apparaissant localement sont dérivés de l'Acide Arachidonique (AA) qui est métabolisée par différentes enzymes (cyclo-oxygénase (COX), lipo-oxygénase (LOX)). L'AA provient de la dégradation des phospholipides membranaires par la phospholipase A2 (80).

Après activation de LOX et COX, la manipulation intestinale conduit à la production d'eicosanoides comme les prostanoïdes (prostaglandines, prostacyclines, thromboxanes) et les leucotriènes. Ces derniers sont synthétisés grâce à l'activation de la LOX alors que les eiconsanoides sont synthétisés par l'activation des COX.

(1) LOX

Le rôle des LOX dans l'iléus a peu été étudié mais les leucotriènes ont un rôle pro-inflammatoire connu. Cependant, d'autres dérivés de l'AA via les LOX tels que les omega-3 acide gras poly-insaturés ont un rôle anti-inflammatoire en produisant de la résolvine, protectine, maresine… (81–83). Il existe plusieurs types de LOX chez l'Homme; LOX-15, LOX12, LOX-5. Chez la souris la LOX 12/15 correspond à la LOX-15 de l'Homme.

Parmi les omega-3 responsables de l'amélioration des fonctions gastro-intestinales, il a été montré qu'une supplémentation alimentaire en acides eicosapentanoiques (EPA) et en acides docosahexaenoiques (DHA) réduisait l'incidence des IPO (84).

Ainsi, dans un modèle murin d'iléus, il a été retrouvé que l'augmentation d'EPA et de DHA est liée à la LOX 12/15 (85). Par ailleurs, la diminution de l'incidence de l'IPO est en rapport avec l'activité de la protectine DX qui diminue l'infiltration des leucocytes dans la *muscularis propria* (85).

(2) COX

Le pic d'augmentation des COX avait lieu 6 heures après le début de la manipulation intestinale (66). Les COX-1 et -2 sont activées par l'interleukine (IL) 1, les lipopolysaccharides bactériens et les facteurs de croissance (86), et permettent de dégrader l'acide arachidonique (AA) en thromboxane A2 et prostaglandine (PG) G puis PGH2 avant elles-mêmes dégradées pour produire des prostacyclines (PGI2) et des prostaglandines (PGE2 et PGD2).

La COX-1 est constitutive dans la paroi intestinale alors que COX-2 est inductible devant une agression. La synthèse de COX-2 peut être induite par les macrophages, les monocytes, les lymphocytes, les fibroblastes, les cellules endothéliales, les neurones ou encore les cellules musculaires lisses vasculaires. Dans le modèle de l'iléus, la synthèse

de COX-2 est augmentée dans les leucocytes phagocytiques de la muscularis propria (87).

COX-1 et COX-2 auraient tous deux un rôle dans l'iléus mais pas par le même biais. En effet, la manipulation intestinale entraine plutôt un excès de synthèse de PG via COX-1 alors que la laparotomie elle-même entraine plutôt une activation de COX-2 (88). Toutefois, dans un modèle d'iléus, l'inhibition exclusive de COX-2 ne permettait pas de restaurer les désordres gastro-intestinaux liés à la laparotomie, alors que l'inhibition exclusive de COX-1 le permettait (89). La COX-1 semble toutefois bien liée à la manipulation intestinale puisqu'elle a été montrée comme ayant un rôle dans la synthèse de PGI2 après traction sur le mésentère (90).

Si le rôle des prostacylines ou de la thromboxane A2 n'a pas été directement étudié dans la littérature, les PG ont fait l'objet de plus d'attention. Il a été montré que la manipulation intestinale lors d'une laparotomie empruntait plutôt la voie de dégradation des PGH2 par la Hematopoietic Prostaglandine D Synthase (HPGDS) ou la Lipocaline-type Prostaglandine D Synthase (LPGDS) pour donner la PGD2. Par ailleurs, la PGH2 est dégradée par la microsomal Prostaglandine E Synthase-1 (mPGES1) en PGE2. Nous avons mis en évidence une association significative entre le taux de HPGDS et la durée de reprise du transit (Résultats 5) et une association non significative entre le taux de mPGES1 et la durée de reprise du transit. Les taux d'enzymes étaient mesurés dans la *muscularis propria* du côlon environ 3 heures après le début de la chirurgie de résection colique pour cancer (Résultats 5). Par ailleurs, l'inhibition pharmacologique de mPGES1 mais pas de HPGDS augmentait la contractilité spontanée du muscle lisse longitudinal colique (Résultats 5). L'augmentation de PGE2 semble être impliquée dans

le mécanisme de l'IPO par le biais des récepteurs EP2 et EP4 (91,92). En effet, une augmentation de ces récepteurs est corrélée à l'augmentation de la durée de reprise du transit. Par ailleurs, cette augmentation est le résultat de la chirurgie (93). L'effet de la PGD2 sur la contractilité du tube digestif est controversé. En effet, elle augmente la contractilité du muscle colique chez le rat (94) mais elle réduit la sensibilité du péristaltisme induit par la pression chez le cochon d'Inde (95).

L'effet des prostaglandines provient d'une inhibition directe sur le muscle circulaire jéjunal (87).

3. Phase III (de résolution)

La phase de résolution est liée à un changement d'expression des cytokines, telles que IL-10, produites par les monocytes infiltrants (96). Elle découle de l'activation du système vagal qui entraine une diminution de l'inflammation au sein de la paroi de l'intestin manipulé. Cette notion de « voie anti-inflammatoire cholinergique » a été introduite par Tracey *et al*. en 2000 (97).

L'activation vagale est liée à l'activation des neurones dans le noyau du tractus solitaire (98), et dans le noyau dorsal du nerf vague (99) par le biais des mécanorécepteurs intestinaux dont le seuil d'activation est alors abaissé (98).

L'effet anti-inflammatoire du système vague provient de l'inhibition de la synthèse de cytokines par les macrophages spléniques via le récepteur alpha7 nicotinique (alpha7 nAChR) (97,100,101) (102) mais le mode d'action du système vagal est discuté. Certaines études suggèrent que l'Ach larguée au niveau des ganglions coeliaques et mésentériques activent les neurones noradrénergiques dans la rate (103) et que c'est à

ce niveau que les cellules T mémoire synthétisent de l'acétylcholine (104). D'autres auteurs rapportent plutôt une action anti-inflammatoire indépendante de la rate, en lien avec l'activation du système nerveux entérique des macrophages de la *musclaris propria* (100).

La réponse vagale provient également de l'activation des macrophages péritonéaux (105). Cette réponse est médiée par STAT 3 et JAK 2. JAK 2 phosphoryle STAT3 (105). STAT3 est par la suite activée par la nicotine dans les macrophages via le récepteur alpha7 nAchR. Cette activation mène alors à une réduction du largage de TNF, MIP 2 et IL-6 sans diminuer le largage de IL-10R (105).

Enfin, une autre voie de stimulation du système vagal est la stimulation du récepteur à la 5-hydroxytryptamine 4 ($5HT_4R$) (106). En effet, les agonistes de la $5HT_4R$ permettent de réduire l'importance de la réponse inflammatoire à la manipulation intestinale et d'améliorer les fonctions intestinales postopératoires en activant l'alpha-7nAChR exprimé par les monocytes/macrophages qui inhibe leur sécrétions de molécules inflammatoires (106).

VI. Modes de prévention

A. Modalités

Plusieurs molécules sont utilisées dans la prévention de l'iléus en pratique courante et agissent sur la phase 1 de l'IPO.

L'Alvimopan est une des molécules les plus étudiées dans la prévention de l'IPO. Non disponible en France, elle agit en antagoniste des récepteurs μ opioïdes. Elle agit en

antagoniste de la morphine ou des endorphines sur le tractus gastro-intestinal. Sept études, en incluant 6 études randomisées ont évalué son efficacité sur la prévention de l'iléus (107–113). L'étude non randomisée montre une amélioration de la tolérance à l'alimentation solide et la récupération de gaz et selles (111). Les résultats des études randomisées sont contradictoires mais il semblerait que l'Alvimopan soit plus efficace en cas d'utilisation conjointe de morphine (60). La dose idéale serait 12 mg d'Alvimopan par jour (107,108,112,114). Une autre étude rapportait des résultats non contributifs dans un contexte d'utilisation de l'Alvimopan à 5 mg/j (110). Enfin, une méta-analyse confirmait que l'Alvimopan réduit la durée de reprise du transit mais l'effet en coelioscopie n'a pas pu être évalué (115)

La Lidocaïne intra-veineuse réduit également la durée de reprise du transit (116). Bien que les protocoles ne soient pas consensuels, les doses injectées sont généralement de 1,5 à 3 mg/kg/h pendant la durée de la chirurgie ou jusqu'à 24 heures après la fin de la chirurgie. Cette effet sur le transit est dépendant de la voie d'administration qui doit être continue et intraveineuse (117). Une récente méta-analyse a montré que la lidocaïne intra-veineuse réduisait la durée de l'IPO mais que les effets secondaires ne sont pas encore suffisamment documentés pour recommander son utilisation en pratique courante (118). De plus, une étude randomisée prospective comparant l'utilisation la lidocaïne intraveineuse ne réduit pas la durée de reprise de transit par rapport à la bupivacaïne épidurale (119).

L'analgésie péridurale (AE) est également utilisée dans l'analgésie postopératoire mais, au regard d'une ancienne méta-analyse (120), son effet sur la motricité gastro-

intestinale n'est pas consensuel. Il reste à noter que toutefois, la définition utilisée pour définir l'iléus était différente selon les auteurs des articles utilisés dans la méta-analyse. Des articles plus récents concluent toutefois que l'AE n'a pas d'intérêt vis à vis de l'iléus postopératoire, dans le contexte de la réhabilitation améliorée et de la chirurgie laparoscopique (121).

Le **propranolol** a été évalué pour prévenir l'iléus postopératoire en agissant sur les fibres bêta-adrénergiques dans une étude randomisée prospective mais aucune modification de l'activité myoélectrique n'a été observée (122).

Deux principaux procédés permettent efficacement de lutter contre l'iléus postopératoire. Leur but est de réduire l'inflammation liée à la manipulation intestinal en réduisant le stress opératoire pour le premier et en agissant directement sur les COX pour le deuxième.

Ainsi, **l'abord coelioscopique (ou laparoscopique)** réduit la manipulation intestinale et améliore la récupération des fonctions gastro-intestinales après chirurgie colorectale ou après cholécystectomie (123–129). Toutefois, au sein d'un programme de réhabilitation améliorée, la coelioscopie ne permet pas, de manière individuelle, de réduire la durée d'hospitalisation ou de l'iléus (130).

Par ailleurs, **les anti-inflammatoires non stéroïdiens** (AINS), en inhibant sélectivement ou non la voie des COX, améliorent la récupération des fonctions gastro-intestinales mais pourraient également augmenter le risque de fistule anastomotique (131,132). Toutefois, une récente méta-analyse conclue à un bénéfice significatif sur les

suites opératoires de l'utilisation de ces AINS dans des protocoles courts, sans pour autant augmenter le risque de fistule (133).

Finalement, le mode de prévention le plus étudié et le plus varié est celui de la stimulation vagale.

Certainement historiquement les plus controversées en raison de la crainte des vomissements, **l'ablation de la sonde nasogastrique** et **la réalimentation précoce** réduisent les complications infectieuses (134), les pertes de nitrogène et diminuent la perméabilité de la barrière intestinale (135). La réalimentation précoce a largement été étudiée en chirurgie colorectale et gynécologique et sa faisabilité n'est plus discutée (134–136)(137–140), même en cas de chirurgie d'urgence (141) ou dans le cadre d'occlusion (142) L'effet sur la reprise du transit est toutefois discuté (139,140).

La nicotine et la mastication par le biais de chewing-gum sont également largement utilisées dans la pratique courante. En mimant, la réalimentation précoce, la mastication de chewing-gum permet de réduire la durée de reprise du transit (143–147). Toutefois, si la mastication permet de réduire la durée du transit, il n'existe pas de protocole consensuel de mastication et, selon les études, les patients mâchent 3 ou 4 fois 15 ou 30 minutes par jour. Le protocole ne semble pas prédictif de l'effet de la mastication.

Récemment, une équipe a proposé l'adjonction de chewing-gums à la nicotine (148), la nicotine ayant un effet anti-inflammatoire (réduction de la TNF, des macrophages…). Il n'y a pour le moment pas de résultats publiés sur les effets de la nicotine sur le transit.

Parmi les autres procédés alimentaires, **l'effet du café** sur la reprise du transit après chirurgie colique a été évalué dans une petite étude randomisée (149). La durée d'hospitalisation ne variait pas mais le délai avant l'évacuation du premier gaz et le délai

avant la tolérance à l'alimentation solide étaient réduits dans le groupe café. **L'administration parentérale d'acides gras poly-insaturés** a été évaluée chez la souris et a permis d'améliorer les fonctions GI postopératoires (84). Enfin, parmi les possibilités de modifications alimentaires, **le Dai-Kenchu-To**, une herbe médicinale japonaise, a un effet anti-inflammatoire partiellement médié par alpha7 nAChR. Plusieurs études ont mis en évidence une amélioration des fonctions GI et de la qualité des premières selles après chirurgie colorectale (150–152).

Sur le plan médicinal, de nombreux **traitements prokinétiques** ont été évalués mais une récente méta-analyse a conclu en l'absence d'effet significatif de ces différents traitements sur les fonctions GI (153).

B. Programmes de réhabilitation améliorée

Les programmes de réhabilitation améliorée se sont généralisés avec l'apparition de la société ERAS (Enhanced Recovery After Surgery) puis du groupe GRACE (Groupe Francophone de Réhabilitation Améliorée Après Chirurgie) dans les pays francophones. Ces programmes associent une quinzaine d'items visant à réduire le stress opératoire et la morbidité opératoire. Les items associés sont, pour la majorité d'entre eux, cités dans les mesures ci-dessus et visent à réduire le stress opératoire, ce qui permet une baisse de l'incidence des IPO.

Les items se répartissent au cours de la période périopératoire :

- *Préopératoire :* immunonutrition, administration *per os* d'hydrates de carbone, information au patient, abstention de la préparation colique, réduction du jeûne pré-opératoire.
- *Peropératoire* : privilégier la coelioscopie, réduire le remplissage peropératoire, éviter le drainage chirurgical, prévenir les nausées et vomissements, administration de dexamétasone peropératoire, ablation de la sonde vésicale en salle opératoire
- *Postopératoire* : réalimentation précoce, mastication de chewing gum, ablation de la sonde urinaire précoce, ablation des cathéters veineux précoce, limitation des apports intra-veineux, mobilisation précoce, antalgie multimodale.

Des études récentes ont mis en évidence une amélioration des fonctions GI après chirurgie abdominale dans le cadre des programmes de réhabilitation améliorée en comparaison avec la prise en charge traditionnelle (6,154–156)

VII. Justification et objectifs de l'étude

Bien que l'efficacité de la réhabilitation améliorée sur l'IPO soit clairement établie, sa mise en œuvre et son impact peuvent encore être améliorés en agissant tant sur le plan clinique que sur la connaissance de son mécanisme d'action.

En effet, sur le plan clinique, il se pose 2 problèmes : le premier étant la faisabilité de la réhabilitation améliorée dans le contexte de patients fragilisés (urgence ou patients âgés) ; le deuxième résidant dans l'absence de consensus entre les différentes équipes au regard de la définition de l'IPO.

Par ailleurs, les programmes de réhabilitation peuvent être améliorés. En effet, les effets de la RA sur les mécanismes physiopathologiques impliqués dans l'IPO restent encore à explorer, en particulier chez l'Homme. D'autre part, bien que ces effets aient été partiellement décrits dans l'intestin grêle, ses mécanismes d'action dans le côlon restent inconnus. Enfin, la capacité d'approches additionnelles à la RA visant à améliorer son efficacité en ciblant des voies d'efficacité thérapeutique de la RA reste aussi à démontrer.

Dans ce contexte général, nous avons organisé notre travail de thèse selon ces deux objectifs principaux. Les premiers travaux (article 1 et 2) sont des travaux principalement cliniques visant à caractériser la faisabilité de la RA dans des situations dites à risques (sujets âgés et situation d'urgence). Dans une partie, nous avons développé des projets de recherche translationnelle adossés/ou non à des études cliniques. En particulier, dans une étude, nous avons caractérisé l'impact de la chirurgie digestive et des programmes de RA sur l'expression de médiateurs lipidiques inflammatoires afin d'identifier de nouveaux facteurs prédictifs d'IPO. Dans une deuxième étude nous avons visé à renforcer l'importance des médiateurs lipidiques

comme cibles thérapeutiques en caractérisant leur modulation par la stimulation tibiale postérieure percutanée. Enfin, dans une dernière partie, nous avons initié le développement d'un modèle préclinique d'IPO afin de pourvoir identifier de nouveaux mécanismes d'action et cibles thérapeutiques d'intérêt.

VIII. Résultats

A. Article 1 publié dans Scandinavian Journal of Surgery

RESUME

Introduction et buts : L'application de la RA chez le sujet âgé doit être évaluée. Notre but était d'étudier les suites opératoires après résection colo-rectale et l'observance des items de la RA chez les patients > 80 ans.

Matériel et méthodes : Tous les patients consécutifs ayant eu une chirurgie colorectale pour cancer dans notre centre sur une période de 19 mois ont été inclus. Tous ont été pris en charge selon le même protocole de RA. Les patients au delà de 80 ans étaient comparés aux plus jeunes.

Résultats : un total de 173 patients était inclus et 36 avaient ≥ 80 ans (20.8%). Les patients ≥ 80 ans avaient un score ASA significativement supérieur à ceux des plus jeunes, et étaient plus opérés en urgence. Durant la période peropératoire, les patients ≥ 80 ans avaient plus de risques d'être opérés en laparotomie que ceux < 80 ans (p=0.048) mais en analyse multivariée, le choix pour la laparoscopie était plutôt influencé par le score ASA < 2 (OR=3.55, IC95% : 1.67 ;7.58) et la chirurgie d'urgence (OR=0.18 ; IC95% 0.06 ;0.50).

Dans la période postopératoire, la stimulation péristaltique et l'ablation de l'abord veineux étaient plus suivis dans le groupe < 80 ans (p=0.012 et p=0.031). Toutefois en analyse multivariée, l'âge n'était pas associé à ces paramètres. La stimulation péristaltique était associée au score ASA ≤ 2 (OR=4.27 ; IC95% :1.18-15.37), de même

que l'ablation du cathéter veineux (OR=2.63 ;IC95=1.33-5.21). La chirurgie urgente avait quant à elle une forte tendance à être associée à ces paramètres (p=0.08).

Conclusion : Bien que l'âge et les comorbidités pourraient affecter l'observance de certaines modalités de la RA, comme l'utilisation du chewing-gum ou l'ablation du cathéter veineux, la RA peut être utilisée après chirurgie colo-rectale chez les patients de plus de 80 ans car elle améliore les suites opératoires et le résultat fonctionnel de la chirurgie.

Original Research Article

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SHORT-TERM OUTCOMES OF COLORECTAL RESECTION FOR CANCER IN ELDERLY IN THE ERA OF ENHANCED RECOVERY

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ABSTRACT

Background and aims: **Early rehabilitation protocols should be assessed in elderly. We aimed to study the outcomes of colorectal surgery and the observance of the modalities of an early rehabilitation protocol in patients over 80 years.**

Material and Methods: **All consecutive patients who underwent surgery for colorectal cancer in our center over a 19-month period were included. All of these patients were managed using the same early rehabilitation protocol. Patients older than 80 were compared to younger patients.**

Results: **A total of 173 patients were included and 36 were ⩾80 years (20.8%). Patients aged ⩾80 years had a significantly higher ASA score and were operated on in emergency. In the peroperative period, patients aged ⩾80 years were more likely to undergo laparotomy than patients <80 years in univariate analysis (p = 0.048), but in multivariate analysis, the choice for a laparoscopy was influenced by ASA score ⩽2 (odds ratio = 3.55, 95% confidence interval = 1.67–7.58) and emergency surgery (odds ratio = 0.18, 95% confidence interval = 0.06–0.50). In the postoperative period, peristalsis stimulation and vascular catheter ablation were significantly better followed in Group 1 (p = 0.012 and 0.031). However, in multivariate analysis, age was not significantly associated with these parameters. Peristalsis stimulation was influenced by ASA score ⩾2 (odds ratio = 4.27, 95% confidence interval = 1.18–15.37) and vascular catheter ablation was also influenced by ASA score ⩽2 (odds ratio = 2.63, 95% confidence interval = 1.33–5.21). Emergency surgery had a strong trend to influence these parameters (p = 0.08).**

Conclusion: **Although age or comorbidities may affect observance for certain modalities such as chewing gum use and vascular catheter ablation, an early rehabilitation protocol can**

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be used after colorectal cancer surgery in patients ⩾80 years old, where it would improve functional results and postoperative outcomes.

Key words: Colorectal surgery; elderly; enhanced recovery program; feasibility; cancer

INTRODUCTION

Surgery with or without associated chemotherapy is the current gold standard for the curative treatment of resectable, non-metastatic colorectal cancer. R1 colonic cancer resection is associated with locally advanced poorly differentiated tumors and an increased rate of recurrence (1). However, in some cases of symptomatic cancer with unresectable metastases, palliative surgery can be proposed. The incidence of colorectal cancer is growing: an estimated 132,700 new cases will occur in 2015 in the United States (2). The world population is growing older, and a recent report from Arai et al. (3) concluded that 13% of the total elderly population is in need of care. Today, physicians frequently encounter patients over the age of 80 with colorectal cancer that should be treated surgically. These elderly patients generally present comorbidities that could contribute to postoperative morbidity and mortality (4). Several studies have shown that laparoscopic surgery provides better postoperative outcomes in elderly patients (5–8). However, the age thresholds at which these advantages manifest remain unclear, and only a few studies have focused specifically on people older than 80. One of those studies reported that perioperative morbidity worsened as performance status increased (9). Others showed that laparoscopic surgery in elderly colorectal cancer patients with poor performance status was safe and not inferior to open surgery (7) and that it was not associated with patterns of death (6).

Although the feasibility and safety of surgery in elderly patients have been confirmed in the literature, the use of early rehabilitation protocols has not been thoroughly examined. Several studies reported that rehabilitation protocols can be implemented in patients aged 65 years and older (10–13), noting that one of those studies identified age >80 as a predictor of delayed mobilization and prolonged hospital stay (12). To the best of our knowledge, only one study, excluding emergency surgery, focused on patients aged 80 years or more (14).

Perioperative early rehabilitation protocols developed and recommended by the Enhanced Recovery After Surgery (ERAS) society (15–18) are associated with shorter hospital stays and lower risks of perioperative complications (19–21), but a number of modalities included in those protocols could be difficult to apply in weak patients, essentially because of standing dogmas among clinicians.

The aim of this work was to study the outcomes of colorectal surgery and the observance of the modalities composing our early rehabilitation protocol in patients aged 80 years or more.

MATERIALS AND METHODS

This is a prospective observational study of a cohort of patients who underwent colorectal resection in one tertiary referral center (Angers University Hospital, Angers, France) between 1 May 2013 and 31 October 2015. The study was approved by the Hospital's Ethics Committee.

All patients who underwent elective or emergency surgery for colorectal cancer were included in this study. Surgical access and tumor location were not exclusion criteria.

An early rehabilitation protocol used in routine practice in our center since December 2012 was implemented for the included patients.

Patients who needed programmed postoperative intensive care were excluded from the study as they did not follow the protocol.

A total of 173 patients were included and a part of them has been included in a previous study in which we showed that enhanced recovery programs reduce the duration of postoperative ileus (22).

Patient data were recorded in a computerized and anonymous database. Data were recorded prospectively for all patients undergoing colorectal surgery, in the aim to provide a regular audit of our practice, as recommended by the ERAS Society. They included (1) clinical characteristics (age, gender, ASA (American Society of Anesthesia) score, comorbidities, treatment and TNM stage), (2) perioperative care items (those from our protocol), and (3) postoperative outcomes (morbidity, delay to flatus recovery, delay to stool recovery, delay to bowel motility recovery, theoretical length of hospital stay, effective length of hospital stay).

Malnutrition was defined as almost one of the three conditions below:

- Serum prealbumin <110 mg/L;
- Serum albumin <30 mg/L;
- Body mass index (BMI) <20 kg/m² if age <70 years or BMI <17 if age >70 years.

Postoperative ileus was defined as the absence of stool recovery associated with vomiting lasting more than 3 days. A nasogastric tube was introduced in case of vomiting.

Morbidity was classified using the Dindo et al. (23) classification. Grade III or greater complications were considered severe.

Theoretical length of hospital stay was defined by the day at which the patient could theoretically be discharged, but was not, because he or she was waiting for a transfer to another department.

TABLE 1
Patient and surgical characteristics.

	Group 1 (G1) Age < 80 years n = 137 (79.2%)	Group 2 (G2) Age ≥ 80 years n = 36 (20.8%)	Overall population n = 173 (100%)	p
Gender				0.20
Male	94 (68.6%)	20 (55.6%)	114 (65.9%)	
Female	43 (31.4%)	16 (44.4%)	59 (34.1%)	
Comorbidities				
Diabetes	18 (13.1%)	4 (11.1%)	22 (12.7%)	1
Arterial hypertension	49 (35.8%)	19 (52.8%)	68 (39.3%)	0.1
Malnutrition	9 (6.6%)	13 (36.1%)	22 (12.7%)	<0.01
ASA score				
1	25 (18.2%)	1 (2.8%)	26 (15%)	0.04
2	66 (48.2%)	11 (30.6%)	77 (44.5%)	0.09
3	37 (27%)	21 (58.3%)	58 (33.5%)	0.001
4	2 (1.5%)	3 (8.3%)	5 (2.9%)	0.062
Treatments				
Antiplatelets	14 (10.2%)	12 (33.3%)	26 (15.0%)	0.013
Corticoids	4 (2.9%)	1 (2.8%)	5 (2.9%)	1
Neuroleptics	7 (5.1%)	1 (2.8%)	8 (4.6%)	1
Anticoagulants	15 (10.9%)	9 (25%)	24 (13.9%)	0.054
>5 medicines	123 (89.8%)	32 (88.9%)	155 (89.6%)	1
Antidiabetics	14 (10.2%)	3 (8.3%)	17 (9.8%)	1
Emergency	15 (10.9%)	6 (16.7%)	21 (12.1%)	0.42
Bowel obstruction	8 (5.8%)	4 (11.1%)	12 (6.9%)	0.28
Procedure				<0.01
Right colectomy	45 (32.8%)	29 (80.5%)	74 (42.8%)	
Left colectomy	26 (19%)	2 (5.6%)	28 (16.2%)	
Sigmoidectomy	51 (37.2%)	3 (8.3%)	54 (31.2%)	
Total colectomy	2 (1.5%)	0	2 (1.2%)	
Anterior resection	11 (8.0%)	1 (2.8%)	12 (6.9%)	
Low anterior resection	2 (1.5%)	1 (2.8%)	3 (1.7%)	

Effective length of hospital stay was defined by the day at which the patient was effectively discharged to home or another institution.

Two groups were defined: Group 1 comprised patients aged less than 80 years and Group 2 those aged 80 years or more.

Categorical data were expressed as percentages and compared using chi-square or Fisher exact tests. Continuous data were expressed as medians (interquartile ranges) and compared using the Mann–Whitney test. The type I error was set to 0.05. Data analyses were performed using SPSS software, version 15 (SPSS, Chicago, IL).

$p < 0.05$ was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

A total of 173 patients, 36 of whom were aged ≥80 years (20.8%), were included in the study (Table 1).

Median ages were 61 years (52; 72) in Group 1 and 85 years (82; 88) in Group 2.

Patients aged ≥80 years had statistically an ASA score higher (ASA, 3–4) ($p < 0.0001$) than patients aged <80 years and had significantly more malnutrition ($p < 0.0001$).

Patients of Group 2 had more frequently a treatment with antiplatelets than patients of Group 1 ($p = 0.013$).

There was a difference as concerns the type of surgical procedure (localization of the colectomy) between the two groups ($p < 0.001$).

EARLY REHABILITATION PROTOCOL MODALITY OBSERVANCE

Observance of protocol modalities in the overall population ranged from 26% to 100% (Table 2).

In the overall population, the median of the compliance of protocol modalities was 14 items. Patients in Group 2 had a significantly poorer peroperative compliancy than Group 1 ($p = 0.03$). Laparoscopy was significantly more often used ($p = 0.046$) in Group 1. In the postoperative period, peristalsis stimulation and vascular catheter ablation were significantly better respected in Group 1 ($p = 0.012$ and 0.031).

POSTOPERATIVE OUTCOMES

Severe complications occurred in 9.8% of the overall patient population (Table 3). There were statistically

TABLE 2
Enhanced recovery program observance.

	Group 1 (G1) Age <80 years n = 137 (79.2%)	Group 2 (G2) Age ≥ 80 years n = 36 (20.8%)	Overall population n = 173 (100%)	p
Preoperative period	∯4 (3; 4)	∯4 (3; 4)	∯4 (3; 4)	0.22
Preoperative counseling	123 (89.8%)	30 (83.3%)	153 (88.4%)	0.38
No fasting∀	86 (70.5%)	22 (73.3%)	108 (71.1%)	0.93
Oral carbohydratesΔ	66 (68%)	16 (72.7%)	82 (68.9%)	0.86
No bowel preparation	121 (88.3%)	35 (97.2%)	156 (90.2)	0.2
Peroperative period	∯6 (5; 6)	∯5 (3,75; 6)	∯5 (4; 6)	0.03
Nausea prevention	69 (50.4%)	17 (47.2%)	86 (49.7%)	0.88
Laparoscopy	104 (75.9%)	18 (50%)	122 (70.5%)	0.046
Nasogastric tube ablation	127 (92.7%)	29 (80.6%)	156 (90.2)	0.052
No abdominal drain	109 (79.6%)	28 (77.8%)	137 (79.2%)	0.99
Intraoperative hypothermia prevention	137 (100%)	36 (100%)	173 (100%)	1
Multimodal analgesia	100 (73%)	21 (58.3%)	121 (69.9%)	0.13
Vascular intake reduction	87 (63.5%)	23 (63.9%)	110 (63.6%)	0.88
Postoperative period	∯5 (4; 6)	∯5 (4; 6)	∯5 (4; 6)	0.06
Early mobilization (operative day£)	36 (26.9%)	9 (25.7%)	45 (26%)	0.93
Early feeding	112 (81.8%)	28 (77.8%)	140 (80.9%)	0.76
Pulmonary physiotherapy	101 (73.7%)	28 (77.8%)	129 (74.6%)	0.78
Vascular catheter ablation	91 (66.4%)	15 (41.7%)	106 (61.3%)	0.012
Foley catheter ablation	118 (86.1%)	28 (77.8%)	146 (84.4%)	0.33
Postoperative vascular intake reduction	110 (80.3%)	24 (66.7%)	134 (77.5%)	0.13
Peristalsis stimulation	129 (94.2%)	30 (83.3%)	159 (91.9%)	0.031
Pre, per, and postoperative period	∯14 (12; 16)	∯13 (11; 15)	∯14 (12; 16)	0.058

∯Median (quartile 1; quartile 3), unit = number of monitored items.
∀n = 152 (n = 122 G1 and n = 30 G2) (exclusion of patients treated in emergency or in obstruction).
Δn = 119 (n = 97 G1 and n = 22 G2) (exclusion of patients treated with gastric emptying disorder, in emergency or in obstruction).
£Missing data n = 4 (n = 3 G1 and n = 1 G2).

TABLE 3
Postoperative morbidity and mortality.

	Group 1 (G1) Age <80 years n = 137	Group 2 (G2) Age ≥ 80 years n = 36	Overall population n = 173	p
Need for nasogastric tube	22 (16.1%)	11 (30.6%)	33 (19.1%)	0.08
Severe complications	13 (9.5%)	4 (11.1%)	17 (9.8%)	0.76
Anastomotic fistula	14 (10.2%)	0	14 (8.1%)	0.044
Postoperative ileus	42 (30.7%)	19 (52.8%)	61 (35.3%)	0.018
Proctorrhagia	8 (5.8%)	1 (2.8%)	9 (5.2%)	0.69
Pneumopathy	5 (3.6%)	2 (5.6%)	7 (4.0%)	0.64
Acute urinary retention	7 (5.1%)	2 (5.6%)	9 (5.2%)	1
Urinary infection	2 (1.5%)	3 (8.3%)	5 (29%)	0.062
Superficial surgical site infection	6 (4.4%)	8 (22.2%)	14 (8.1%)	0.002
Death	1 (0.7%)	2 (5.6%)	3 (1.3%)	0.11

significant differences between the outcomes, in terms of postoperative ileus and superficial surgical site infection (p = 0.018 and 0.002) what Group 2 was more likely to experiment.

One patient died in Group 1 (0.7%) and two (5.6%) in Group 2.

DELAY TO BOWEL MOTILITY RECOVERY AND LENGTH OF HOSPITAL STAY

The median delay to gas recovery (2 days (1; 2) in Group 1 vs 2 days (1; 3) in Group 2) was not significantly different between the two groups (p = 0.07) and the median delay to stool recovery (3 days (2; 4) in Group 1 vs 3 (2; 5) in Group 2) (p = 0.11) was not too.

The median effective lengths of hospital stay were 6 days (4; 9) for Group 1 and 11 days (7.25; 14.5) for Group 2 (p < 0.001). The median theoretical lengths of hospital stay were 5 days (4; 8) for Group 1 and 8 days (5; 11.75) for Group 2 (p = 0.008).

UNEXPECTED REHOSPITALIZATION

There were 2 rehospitalizations in Group 2 and 10 in Group 1 (p > 0.5) (12 patients on 134 (9%) for the overall population).

TABLE 4

Multivariate analysis of different items of the enhanced recovery program that differed between the patients ⩾ 80 years and the patients <80 years in univariate analysis.

	OR	95% CI	p
Immediate NGT removal			
Emergency surgery	0.43	0.12–1.51	0.19
ASA Score 1–2	1.61	0.54–4.80	0.39
Age ⩾ 80	0.41	0.13–1.26	0.12
Laparoscopic use			
Emergency surgery	0.18	0.06–0.50	0.001
ASA Score 1–2	3.55	1.67–7.58	0.001
Age ⩾ 80	0.48	0.21–1.14	0.099
Compliance with peristalsis stimulation			
Emergency surgery	0.30	0.08–1.14	0.08
ASA Score 1–2	4.27	1.18–15.37	0.03
Age ⩾ 80	0.54	0.16–1.84	0.32
Compliance with vascular catheter removal			
Emergency surgery	0.42	0.16–1.12	0.08
ASA Score 1–2	2.63	1.33–5.21	0.01
Age ⩾ 80	0.52	0.23–1.16	0.11

NGT: NasoGastric Tube; OR: odds ratio; CI: confidence interval.

MUTLIVARIATE ANALYSIS

In multivariate analysis, age ⩾80 years did not significantly influence laparoscopic use (p = 0.10), compliance with vascular catheter ablation (p = 0.11), compliance with peristalsis stimulation use (p = 0.32), or compliance with immediate nasogastric tube removal (p = 0.12; Table 4).

ASA score ⩽2 significantly influenced peristalsis stimulation compliance (odds ratio (OR) = 4.27; 95% confidence interval = 1.18–15.37), laparoscopic use (OR = 3.55; 95% confidence interval = 1.67–7.58), or vascular catheter ablation (OR = 2.62; 95% confidence interval = 2.63–1.33), whereas emergency surgery significantly influenced laparoscopic use (OR = 0.18; 95% confidence interval = 0.06–0.50; Table 4).

DISCUSSION

Among the 173 patients included in this cohort, 36 (20.8%) were 80 years or older. In this more elderly population, protocol modality compliance ranged from 25% to 100%.

A recent report focusing on patients aged 65 years or more showed rates of protocol modality compliance between 28% and 87% (10). More recently, Pedziwiatr et al. (14) reported no difference of compliance between a group of patients >80 years and a group of patients <50 years, apart from opioids consumption. They reported more than 80% of compliance in overall population and did not report any difference between groups. We report compliance lesser than this probably because we assessed 18 items (78% were followed in group 1 whereas 72% were in group 2 (p > 0.05)). This difference of compliance may probably be due to the fact that we also included emergency surgery that was excluded by Pedziwiatr et al. Indeed, emergency surgery is known to provide lesser compliance than elective surgery (10), and we found a significant influence of emergency surgery on laparoscopic use (p = 0.001) and a strong trend of its influence on compliance with vascular catheter ablation and peristalsis stimulation (p = 0.08 and 0.08).

Another report stated that very elderly should be considered after 75 years and authors also concluded in the feasibility of enhanced recovery programs over 75 years (24). Our results agreed with the literature because no impact of age was found in multivariate analysis, when age was corrected by ASA score and emergency surgery.

In colorectal populations irrespective of age, Ahmed et al. (25,26) reported protocol modality compliance rates ranging from 25% to 100%, while pointing out that the implementation of certain modalities of early rehabilitation protocols is difficult outside of the clinical study setting (25,26). Our rates of compliance are in accordance with the literature.

Furthermore, in our study, the compliance rates for two modalities differed significantly between Group 1 (age <80 years) and Group 2 (age ⩾80 years) in univariate analysis. Indeed, the rate of chewing gum use in the postoperative phase differed from 83.3% for Group 2 to 94.2% for Group 1 (p = 0.031), but in multivariate analysis, only ASA score was significantly associated (OR = 4.27; p = 0.03). Chewing gum has been shown to fasten the recovery of bowel motility (27), but in weaker patients, this modality may not be applicable due to poor oral health, the presence of dental prostheses, or the severity of comorbidities (chronic obstructive bronchopneumopathy).

The other difference between the two groups is the early vascular catheter ablation that was more likely to be followed in younger patients in univariate analysis but not in multivariate analysis in which ASA score was the only factor significantly associated with the compliance with this item (OR = 2.63; p = 0.01). This is probably due to the fear of early complications or the need of treating early complication such as postoperative delirium. Indeed, Raats et al. (28) recently reported a 21% incidence rate for postoperative delirium after colorectal surgery and that this complication occurred in patients with a median age of 82 years. We did not specifically record this complication in our study, but within this dynamic may lie an explanation for the difference in early vascular catheter ablation compliance between our two groups.

Our study does have several limitations. First, a control group of patients aged ⩾80 years would have been of interest for our study. However, we did compare this age group to a younger group and found no important differences in characteristics between them, apart from the age.

Also, our compliance rates can be slightly lesser than those reported in the literature, but this is probably because we decided to include patients undergoing urgent surgery. This draws a better picture of our practice, and this is more representative of the population.

Literature is weak on feasibility, compliance, and safety of enhanced recovery programs in elderly, and the need of cohort studies is important. Our results should help and reassure physicians in their choice to implement an early rehabilitation protocol for elderly patients.

Finally, results regarding malnutrition should be considered with caution because our definition did not take into account loss of weight because of a higher part of missing data due to the retrospective characteristic of this study. However, despite this limitation, our results showed a higher proportion of malnutrition in elder patients, as it is reported in the literature (29), and should awake the physician to the potential higher risk of postoperative morbidity of these patients, already at risk of morbidity due to their higher rate of comorbidities.

CONCLUSION

Age significantly influenced compliance with vascular catheter removal and peristalsis stimulation in univariate analysis but not in multivariate analysis. Differences observed in univariate analysis were due to ASA score difference between the two groups of age. However, age is not a brake to enhanced recovery programs application, but these programs should be adapted to ASA score to suit perfectly to patient individuality and to be performed safely.

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RESUME

Introduction : Les occlusions coliques d'origine maligne nécessitent fréquemment un recours vers la chirurgie. La compliance à la RA y est réduite du fait de la non-ablation de la sonde nasogastrique (SNG) dans la période postopératoire immédiate. Le premier but de cette étude était de rechercher des facteurs associés avec l'échec de l'ablation immédiate de la SNG chez les patients ayant eu une chirurgie d'occlusion colique maligne en urgence. Le second but était d'évaluer la morbidité en lien avec la réinsertion de la SNG.

Matériel et méthodes : Cette étude rétrospective et monocentrique incluait tous les patients consécutifs admis pour une occlusion colique d'origine maligne, et qui ont nécessité une prise en charge chirurgicale. Les patients non opérés initialement ont été exclus (n=178 ;69.3%). Le groupe de patients nécessitant la réinsertion de la SNG était comparé à ceux n'en ayant pas eu besoin.

Résultats : Soixante-dix-neuf patients ont nécessité un recours à la chirurgie, parmi lesquels 18 (22.8%) ont nécessité une repose de la SNG. Il n'y avait pas de différence entre les groupes en ce qui concerne l'ablation immédiate de la sonde nasogastrique (p=0.87), ou l'inclusion dans un programme de RA (p=0.75). Toutefois, une dilatation préopératoire de l'intestin grêle était associée à une diminution de la nécessité de la repose de la SNG (p=0.04). Par ailleurs, une tumeur localisée à gauche était associée à une augmentation de la repose de la SNG en analyse uni- (p=0.034) ou multivariée (OR=8 ; $p<0.05$).

L'abord chirurgical et le type de chirurgie n'étaient pas associés avec la réinsertion de la SNG. Enfin, la période postopératoire influençait la réinsertion de la SNG puisque elle

était associée à l'IPO (OR= 4 ; p<0.05) et la morbidité postopératoire (OR=4 ; p<0.05). En revanche la morbidité n'était pas associée à une ablation précoce de la SNG.

Conclusion : La repose de la SNG n'était pas influencée par son ablation immédiatement après la chirurgie. Les tumeurs situées à gauche et les patients à risque d'IPO doivent être pris en charge avec attention. L'ablation immédiate de la SNG n'est pas contre-indiquée en cas d'occlusion intestinale colique néoplasique car elle n'entraîne pas une augmentation de la morbidité et n'est pas associée à une augmentation du risque de repose.

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ORIGINAL SCIENTIFIC REPORT

Primary Surgery for Malignant Large Bowel Obstruction: Postoperative Nasogastric Tube Reinsertion is Not Mandatory

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Abstract

Background Malignant large bowel obstructions frequently require emergency surgery. Compliance with enhanced recovery after surgery programmes is significantly reduced due to non-removal of the nasogastric tube in the postoperative period. The first aim of the present study was to research factors associated with the failure of immediate nasogastric tube removal in patients who had undergone emergency surgery for malignant large bowel obstruction. The second aim was to assess the morbidity linked to nasogastric tube reinsertion.

Methods This retrospective and monocentric study included all consecutive patients admitted for acute malignant large bowel obstruction who underwent emergency surgery. Patients who were not primarily operated on were excluded ($n = 178$; 69.3%). The group of patients requiring nasogastric tube (NGT) reinsertion was compared with the group that did not require NGT reinsertion.

Results Seventy-nine patients underwent emergency surgery, of which 18 (22.8%) required nasogastric tube reinsertion. There was no difference between the two groups with regard to (a) immediate nasogastric tube removal ($p = 0.87$) and (b) inclusion in an enhanced recovery programme ($p = 0.75$). However, preoperative small bowel dilatation was associated with a reduction in the need for NGT reinsertion ($p = 0.04$). A left-sided tumour was also associated with the need for NGT reinsertion in uni- ($p = 0.034$) and multivariate analysis (OR = 8; $p < 0.05$). Surgical access and procedure were not significantly associated with NGT reinsertion. The postoperative course influenced NGT reinsertion, which was significantly associated with postoperative ileus (OR = 4; $p < 0.05$) and postoperative morbidity (OR = 4; $p < 0.05$). Morbidity was not linked to nasogastric tube removal.

Conclusion Nasogastric tube reinsertion was not affected by immediate removal of the tube. Left-sided tumours and patients at risk of postoperative ileus should be managed with caution. Immediate nasogastric tube removal is not contraindicated in the case of large bowel obstruction because it is not associated with a higher risk of NGT reinsertion.

Introduction

Malignant large bowel obstruction occurs in 8–29% of colonic tumours [1, 2]. In the case of right-sided tumours, surgery is mandatory. This is because a self-expanding metallic stent (SEMS), as a "bridge to surgery", has not been proven as more advantageous than surgery itself [3]; carcinologic right colectomy is recommended. In the case of left-sided tumours, there is a lack of consensus and SEMS can be used as a bridge to surgery. However,

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surgery can be performed safely and with the same outcomes as elective surgery, according to certain authors [4].

In the case of elective surgery, enhanced recovery after surgery management could reduce postoperative morbidity [5], as in the case of emergency surgery [6]. Nevertheless, there is a dogmatic belief that reduces compliance with these programs. Roulin et al. [7] showed that immediate postoperative removal of the nasogastric tube was observed significantly less often in emergency surgery than in elective surgery. Nasogastric tube removal is mandatory to ensure correct compliance with enhanced recovery programmes. Indeed, if the tube is left in place, patients cannot eat or drink and the intravenous catheter cannot be removed.

Dogmatic beliefs advocating the non-removal of the nasogastric tube are based on fear of the need for nasogastric tube reinsertion and, moreover, the fear of pulmonary inhalation. This fear is unfounded, however. Indeed, the nasogastric tube can lead to micro-pulmonary inhalation or oesophageal irritation, which negatively affects the postoperative course [8].

There is sufficient evidence in the literature to recommend nasogastric tube removal in the immediate postoperative course following elective colorectal surgery [9]. However, there does not appear to be any specific report aimed at assessing the feasibility of immediate postoperative nasogastric tube removal in the case of emergency surgery.

The first aim of this study was to research factors associated with the failure of immediate nasogastric tube removal in patients who underwent emergency surgery for malignant large bowel obstruction and consequently required nasogastric tube reinsertion. The second aim was to assess the morbidity linked to nasogastric tube reinsertion.

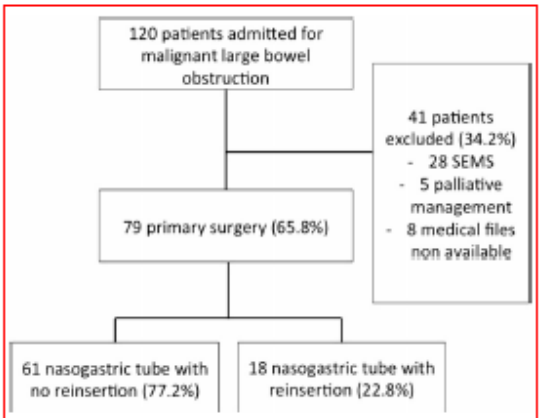


Fig. 1 Flow chart of the population included in the study

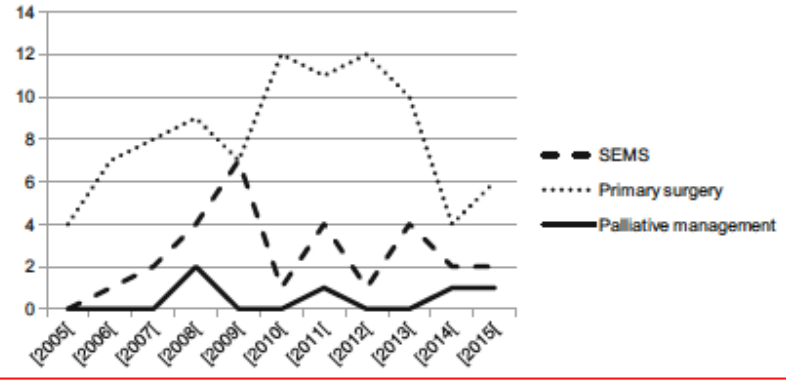
Materials and methods

A retrospective study was conducted from 2005 to 2015, with 120 patients admitted with a diagnosis of acute colonic obstruction. Seventy-nine patients underwent primary surgery (65.8%) and were included in this study (Fig. 1).

Primary surgery was defined as emergency surgery for malignant large bowel obstruction. Surgical procedures included were: colonic resection (with or without anastomosis), colostomy and internal derivation. Surgical access was not an exclusion criterion. The trends for the management of patients admitted with a diagnosis of acute colonic obstruction are reported in Fig. 2.

Patients treated from 2005 to June 2013 were managed in a conventional way, whereas those treated from June 2013 onwards were managed with an enhanced recovery after surgery programme. Following the

Fig. 2 Trends of management of the patients admitted for malignant large bowel obstruction, according to the year of admission



implementation of enhanced recovery programmes, the practice of immediate nasogastric tube (NGT) removal became a standard procedure for all colorectal surgery.

Patients who underwent preoperative obstruction clearance with a self-expandable metallic stent (SEMS) and patients who underwent palliative management were excluded from the study.

Demographic data, surgical management data and postoperative course data were collected retrospectively.

Data collected were:

1. Demographic (gender, age, medical and surgical history, comorbidities and tumour characteristics).
2. Related to surgical management (procedure, surgical access, need for stoma, anastomosis confection, immediate nasogastric tube removal).
3. Related to the postoperative course (morbidity, postoperative ileus occurrence, inclusion in an enhanced recovery programme, delay for gas and stool recovery, need for nasogastric tube reinsertion).

Postoperative ileus was defined by at least two of the five following symptoms, after postoperative day 4 [10]:

- Nausea or vomiting over the preceding 12 h.
- Inability to tolerate a solid or semisolid oral diet over the preceding two mealtimes.
- Abdominal distension.
- Absence of flatus and stool over the preceding 24 h.
- Radiologic evidence of ileus on abdominal plain film or CT over the preceding 24 h.

Immediate nasogastric tube removal was defined as the removal of the nasogastric tube immediately after the removal of the orotracheal tube, in the recovery room.

Severe morbidity was defined as the occurrence of a postoperative complication, classified as grade 3 and over according to the Clavien–Dindo classification [11].

Two groups of patients were defined. The NGT group was the group of patients who required nasogastric tube reinsertion. The NNGT group did not require nasogastric tube reinsertion.

Indication for reinsertion was left to the surgeon's discretion. However, the usual practice is to reinsert the nasogastric tube if the patient experiences recurrent vomiting associated with abdominal distension.

Indication for removal of the nasogastric tube was also left to the surgeon's discretion. However, the usual practice is to remove the tube after the first flatus, if the nasogastric tube has aspired less than 200 cc of gastric secretions. Only removals based on medical prescription were taken in account. Accidental or deliberate removal was not included in this category because NGTs were systematically reinserted until the surgeon decides to remove it.

Statistical analysis

Categorical data were expressed as percentages and compared using the Chi-square test or Fisher's exact test. Continuous data were expressed as medians (interquartile ranges) and compared using the Mann–Whitney test. The type I error was set to 0.05. Data analyses were performed using SPSS software, version 15 (SPSS, Chicago, IL). $p < 0.05$ was considered to be statistically significant.

Results

Seventy-nine patients underwent primary surgery for malignant colonic obstruction (Fig. 1).

Among them, 16 patients followed a programme of enhanced recovery after surgery (20.2%) and eight patients underwent immediate nasogastric tube removal (10.1%). Eighteen patients required nasogastric tube reinsertion (22.8%).

Patient and tumour characteristics

There was no difference with regard to patient characteristics between the two groups (Table 1).

While the left side was the main location of the tumour in the study population ($n = 50$, 60.3%), it was also the predominant tumour location in patients who required nasogastric tube reinsertion ($n = 16$, 88.9%). This location was found to be significantly different between the two groups ($p = 0.034$).

Preoperative imaging was associated with the need for nasogastric tube reinsertion. In the event of a lack of small bowel dilatation, the need for a nasogastric tube increased ($p = 0.04$).

Preoperative and postoperative short course

The surgical procedure was not significantly different between the two groups ($p = 0.18$). The confection of anastomosis was not associated with the need for nasogastric tube reinsertion ($p = 0.3$).

Interestingly, immediate removal of the nasogastric tube and inclusion in enhanced recovery programmes were not associated with the need for nasogastric tube reinsertion ($p = 0.87$).

In the postoperative course, ileus and severe morbidity were associated with the need for nasogastric tube reinsertion (respectively, $p = 0.01$ and $p = 0.034$).

Delay to first flatus was not significantly associated with the need for nasogastric tube reinsertion (0.15). However, a higher delay to stool recovery was associated with a need for reinserting the nasogastric tube ($p = 0.045$).

Table 1 Demographic characteristics, preoperative course and short-term postoperative outcomes of patients undergoing emergency surgery for malignant large bowel obstruction

	NNGT ($n = 61$)	NGT ($n = 18$)	Overall population	p
Male gender [n (%)]	29 (47.5%)	11 (61.1%)	40 (50.6%)	0.31
Median of age (year)	76 (66;84)	73.5 (66;81)	75 (66;84)	0.6
Median of BMI (kg/m^2)	25.25 (22;28)	26 (23.4;29)	25.2 (28;22)	0.37
ASA score [n (%)]				0.56
ASA 1	10 (16.4%)	3 (27.3%)	13 (16.4%)	
ASA 2	16 (26.2%)	5 (27.8%)	11 (13.9%)	
ASA 3	28 (45.9%)	10 (55.6%)	38 (48.1%)	
ASA 4	7 (11.5%)	0	7 (8.9%)	
Medical history				
Diabetes	9 (14.8%)	5 (27.8%)	14 (17.7%)	0.91
Arterial hypertension	28 (45.9%)	8 (44.4%)	36 (45.6%)	>0.5
Atrial fibrillation	3 (5%)	2 (11.1%)	5 (6.4%)	0.33
Surgical history [n (%)]				
Laparotomy	25 (41%)	7 (38.9%)	32 (40.5%)	0.87
Laparoscopy	2 (3.3%)	1 (5.6%)	3 (3.8%)	0.16
Tumour location [n (%)]				**0.034**
Right	20 (32.8%)	1 (5.6%)	21 (26.6%)	
Transverse	7 (11.5%)	1 (5.6%)	8 (10.1%)	
Left, sigmoid	34 (55.7%)	16 (88.9%)	50 (63.3%)	
Surgical procedure				0.18
Left colectomy	14 (23%)	8 (44.4%)	22 (27.8%)	
Right colectomy	18 (29.5%)	1 (5.6%)	19 (24.1%)	
Hartman's procedure	5 (8.2%)	3 (16.7%)	8 (10.1%)	
Subtotal colectomy	10 (16.4%)	4 (22.2%)	14 (17.7%)	
Derivation colostomy	7 (11.5%)	2 (11.1%)	9 (11.4%)	
Right colectomy with no anastomosis	2 (3.3%)	0	2 (2.5%)	
Internal derivation	5 (8.2%)	0	5 (6.4%)	
Laparoscopic access	3 (4.9%)	2 (11.1%)	5 (6.4%)	0.34
Protective enterostomy	4 (6.6%)	1 (5.6%)	5 (6.4%)	>0.5
Terminal enterostomy	16 (26.2%)	7 (38.9%)	23 (29.1%)	0.3
Immediate postoperative nasogastric tube removal	6 (9.8%)	2 (11.1%)	8 (10.1%)	0.87
Postoperative course				
Overall morbidity	41 (67.2%)	17 (84.4%)	58 (73.4%)	**0.03**
Severe morbidity	12 (19.7%)	8 (44.4%)	20 (25.3%)	**0.034**
Postoperative ileus	4 (10.8%)	14 (35.9%)	18 (23.7%)	**0.01**
First flatus (days)	3 (2;4)	3.5 (3;5)	3 (2;4)	0.15
First stool (days)	3 (2;5)	4 (3;5.75)	3.5 (2;5)	**0.045**
Length of stay	14 (12;19)	19 (15;28)	15 (12;21)	**0.02**
Enhanced recovery programme inclusion	12 (19.7%)	4 (22.2%)	16 (20.3%)	0.75
Early refeeding	7 (11.5%)	1 (5.6%)	8 (10.1%)	0.67
Preoperative Imaging				
Small bowel dilatation	40 (65.6%)	7 (38.9%)	47 (59.5%)	**0.04**
Caecal dilatation	32 (53.3%)	10 (55.6%)	42 (53.8%)	0.87

Significant results in bold

Table 2 Multivariate analysis of factors associated with the need for nasogastric tube reinsertion

	Odds ratio	95% Confidence interval	*p*
Small bowel dilatation	0.6	0.2–2.1	0.4
Postoperative ileus	4.4	1.1–17.3	0.03
Severe morbidity	4.7	1.2–18.3	0.03
Left-sided tumour	8	1.3–48.5	0.02

Morbidity

Among patients with severe morbidity, six experienced acute respiratory distress syndrome (3 due to inhalation pneumopathy). Among these patients, none underwent immediate nasogastric tube removal and three required nasogastric tube reinsertion.

Other patients experienced anastomotic leakage ($n = 4$), evisceration ($n = 2$), parietal abscess ($n = 1$), delirium tremens ($n = 2$), obstructive renal failure ($n = 1$), melena ($n = 1$), severe natremia disorder ($n = 1$), heart attack ($n = 1$), hypovolemic shock ($n = 1$), decompensation by ascites ($n = 1$), iatrogenic pneumothorax ($n = 1$).

The mortality rate was 8.8% ($n = 7$).

The need for nasogastric tube reinsertion was associated with an increased length of hospital stay ($p = 0.02$).

Multivariate analysis

In multivariate analysis (Table 2), a left-sided tumour (OR = 8;95% CI 1.3–48.5), postoperative ileus (OR = 4;95% CI 1.1–17.3) and severe complications (OR = 4;95% CI 1.2–18.3) were significantly associated with the need for nasogastric tube reinsertion. Small bowel dilatation was associated with a reduction in the need for nasogastric tube reinsertion.

Discussion

Among the consecutive patients admitted for colonic obstruction due to a malignant colonic tumour and included in our study, at least 65.8% underwent primary surgery. This percentage is lower than what is reported in the literature; Zaher Moola et al. [12] reported that 80% of patients were treated with primary surgery and 18% of patients were treated using a stent. This difference is probably because the team participating in the present study was involved in the early uses of stenting as a "bridge to surgery" [13]. Following discussion about the deterioration of a potential prognosis due to stent use [14, 15], it was decided that primary surgical management would again become the preferred treatment method.

The team taking part in this study was involved in a large programme of enhanced recovery after surgery. However, only 8 of the 16 patients meant to follow the protocol underwent immediate postoperative removal of the nasogastric tube, which confirmed the difficulty of challenging dogmatic beliefs. Indeed, early removal of the nasogastric tube has been reported in the literature as being safe in the event of elective colorectal surgery [9], but there is no further information regarding emergency surgery. With regard to enhanced recovery after surgery programmes, Lohsiriwat [6] focused on patients undergoing colorectal surgery for malignant large bowel obstruction; the author reported a significant reduction in their length of stay in hospital, but no significant reduction in morbidity. However, he did not report on the rate of compliance with the programmes.

Roulin et al. [7] reported a significant reduction in compliance with regard to nasogastric tube removal after emergency colorectal surgery compared to elective surgery. Understandably, there was a significant reduction in compliance with postoperative oral nutrition supplementation, a reduction in postoperative intravenous fluids and an increase in oral fluid intake. This supports the importance of early postoperative nasogastric tube removal to ensure compliance with enhanced postoperative recovery programmes.

In the cohort reported here, the nasogastric tube was removed early in eight patients (10.1%) and did not have any impact on the need for nasogastric tube reinsertion ($p = 0.87$). Moreover, inclusion in an enhanced recovery protocol was not associated with this need.

On the contrary, some surprising factors were found to be associated with the need for nasogastric tube reinsertion, such as a left-sided tumour (OR = 8). This differs from elective surgery, in which a right-sided tumour seemed to be associated with a higher risk of postoperative ileus [5]. No formal explanation for this can be offered. However, it could be due to the fact that the diagnosis of a malignant obstruction caused by a left-sided tumour usually occurs after a longer period of development, as opposed to a right-sided tumour which leads to early small bowel dilatation. The latter is associated with nausea and vomiting and, as a result, faster management. This could also explain the fact that preoperative small bowel distension is not associated with the need for nasogastric tube reinsertion.

Furthermore, a longer delay in diagnosis is likely to lead to transitional colonic muscle paresis.

On the contrary, certain factors, such as the occurrence of postoperative ileus, are associated with the need for nasogastric tube reinsertion (OR = 4). However, known risk factors for postoperative ileus, such as the need for

enterostomy [16, 17] or laparotomy [18], were not associated with the need for nasogastric tube reinsertion. This is probably because postoperative ileus can have different grades of severity and not every patient required nasogastric tube reinsertion.

Moreover, it is interesting to note that there was no difference in the median of delay before first flatus between the two groups ($p = 0.15$), whereas there was a significant difference in the median of delay before first stool ($p = 0.045$). This highlights the fact that gas is not a reliable indicator for gastrointestinal motility recovery and that the endpoint that should be used to attest this recovery is the one proposed by Van Bree et al. [19].

Finally, the need for nasogastric tube reinsertion was associated with morbidity ($p = 0.03$), especially severe morbidity (OR = 4). Morbidity included postoperative ileus, and it is therefore logical that it is associated with a need for nasogastric tube reinsertion. However, with regard to severe morbidity, certain pulmonary complications (such as pulmonary inhalation) were probably consequences of postoperative ileus [20] and therefore of nasogastric tube reinsertion. Non-pulmonary complications (such as evisceration, fluid and electrolyte imbalance and anastomotic leakage) are also known to be associated with postoperative ileus [20–22], which explains the association with the need for nasogastric tube reinsertion.

This study presents several limitations that are inherent to its retrospective nature. Indeed, certain information, such as the delay between the appearance of symptoms and surgery or nutritional symptoms, could be associated with the need for nasogastric tube reinsertion. The number of patients in whom the nasogastric tube had been removed immediately after surgery is limited. However, the study allows multivariate analysis and makes some positive conclusions that could improve dogmatic beliefs and enhance the management of patients undergoing emergency surgery for malignant large bowel obstruction.

Conclusion

Enhanced recovery programmes did not lead to a higher rate of nasogastric tube reinsertion compared to traditional management of patients after surgery for obstructed colorectal cancer (nasogastric tube left in place after surgery). Our results support the safety of nasogastric tube removal in the case of surgery for malignant colonic obstruction. However, left-sided tumours and patients at risk of postoperative ileus should be managed with caution. Consideration of nasogastric tube reinsertion should take into account associated postoperative complications. Nevertheless, our conclusions present a low level of evidence and should be confirmed in a large-size effective prospective study.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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La réhabilitation améliorée est connue pour améliorer les suites opératoires après chirurgie, notamment en terme de durée d'hospitalisation et de réduction du taux de fistules anastomotiques (157). Ces protocoles de réhabilitation ont été introduits au cours de la dernière décennie avec un succès majeur dans la chirurgie programmée. Par le biais de **l'article 1 et 2**, nous avons pu montrer que ces programmes étaient applicables également dans le contexte de la chirurgie chez le sujet âgé, mais aussi dans le contexte de la chirurgie d'urgence.

L'impact de la RA sur l'IPO n'ayant pas été spécifiquement évalué dans la littérature, dans l'article 3, nous avons étudié l'impact de la RA sur les fonctions gastro-intestinales.

C. Article 3 publié dans le Journal of Visceral Surgery

RESUME

Introduction: Si l'intérêt de la réhabilitation améliorée dans la chirurgie colorectale a pu être prouvé sur la morbidité et la durée d'hospitalisation postopératoire, son impact sur la durée de reprise du transit est peu documenté. Les objectifs étaient d'évaluer l'impact de la réhabilitation améliorée sur la reprise du transit, et d'évaluer l'importance de la définition de l'iléus et son incidence rapportée dans la littérature.

Matériel et méthodes : Il s'agit d'une étude observationnelle prospective monocentrique portant sur tous les patients consécutifs opérés d'une anastomose colo-rectale sur 17 mois. La reprise d'un transit global était définie par la récupération d'un transit de matière associé à la tolérance à l'alimentation solide.

Résultats : 131 patients étaient inclus avec une adhésion médiane de 14 (13 ;16) items suivis sur les 19 traceurs. Le délai médian de reprise du transit gazeux était de 2 jours alors que le délai de reprise d'un transit de matière était de 3 jours. Le délai de reprise d'un transit gazeux ainsi que d'un transit global diminuait quand l'observance au protocole augmentait (respectivement $p<0.001$; $r2=0.11$ et $p=0.04$; $r2=0.06$). L'incidence de l'iléus était de 1,5 à 61,8% en fonction de la définition (cut-off de 1 à 7 jours). Une observance au protocole ≥85% protégeait de l'apparition de l'iléus ≥4 jours (OR=0.35 ;IC95%=0.15-0.83).

Conclusion : la mise en place et l'observance d'un programme de réhabilitation améliorée après chirurgie permettait une diminution du délai de reprise du transit mais une définition consensuelle de l'iléus est nécessaire.

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ORIGINAL ARTICLE

Does enhanced recovery reduce postoperative ileus after colorectal surgery?

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KEYWORDS
Improved rehabilitation;
Enhanced recovery after surgery;
Colorectal surgery;
Postoperative ileus;
Intestinal motility

Summary
Introduction: While enhanced recovery after surgery (ERAS) has been proven to improve results in colorectal operations with regard to morbidity and duration of hospital stay, its impact on recovery of bowel motility is poorly documented. The aims of this study were to assess the impact of ERAS on bowel motility recovery, and to assess the consequences of the definition of postoperative ileus on its reported incidence in the literature.
Material and methods: This is a single-center prospective observational study of consecutive patients who underwent colorectal resection with anastomosis over a period of 17 months. Global resumption of intestinal transit (GROT) was defined as passage of stool combined with alimentary tolerance of solid food.
Results: One hundred and thirty-one patients were included. A median of 14 items (range: 13–16) was complied out of 19 observable items in the protocol. Median time to passage of flatus (MTPF) was 2 days and the GROT was 3 days. The time interval to MTPF as well as to GROT decreased as adherence to the ERAS protocol increased (respectively $P < 0.001$, $r^2 = 0.11$ and $P = 0.04$, $r^2 = 0.06$). The incidence of postoperative ''ileus'' varied from 1.5% to 61.8% depending on the interval chosen to define ileus (cut-off from 1 to 7 days). Adherence to $\geq 85\%$ of the items in the ERAS protocol protected patients from ''prolonged ileus'', i.e., lasting ≥ 4 days (OR = 0.35; 95% CI = 0.15 to 0.83).
Conclusion: The implementation of and compliance with an ERAS protocol allowed a reduction in the time to GROT. There is a need for a consensual definition of postoperative ileus.

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Introduction

Postoperative ileus is currently a real problem in surgery since it results in increased hospital costs, particularly for colorectal surgery, and also because it is responsible for an increase in postoperative morbidity and patient discomfort during the period before resumption of intestinal transit (ROT) [1,2].

Since the reports of Kehlet and Fearon et al. [3,4], many studies have investigated the benefit of multidisciplinary management to improve postoperative rehabilitation [5–7] as recommended by the ERAS® Society (Enhanced Recovery After Surgery) [8,9] and by GRACE [10], for colorectal, urologic, orthopedic, gynecologic or major vascular surgery. While the utility of ERAS for colorectal surgery has been clearly demonstrated with regard to reduction of duration of hospitalization [6–8], to improvement of quality of life in the perioperative period [11], and to a decrease in the overall cost of care [12], its impact on decreasing duration of postoperative ileus has not been amply documented.

Whereas there are no consensual criteria for assessing ROT (time interval to passage of flatus, to removal of nasogastric [NG] tube, to passage of stool), Vather et al. have proposed a definition of ileus based on the presence of at least two of five proposed criteria [13]. Van Bree et al. later confirmed the primary endpoint of ROT as passage of stool in association with tolerance of a solid diet [14]. However, there is no consensus regarding what constitutes a normal interval for ROT since, according to various authors, a normal time limit for ROT is arbitrarily placed between 3 and 7 days [13,15–20]. This lack of consensus leads to a bias that makes comparison of these studies impossible.

The main aim of this study was to evaluate the impact of ERAS on ROT in the postoperative period after colorectal surgery. The secondary objective of this study was to assess the importance of the definition of ileus in relation to its reported incidence in the literature.

Material and methods

Patients

This is an observational prospective single-center study conducted between July 1, 2013 and January 1, 2015 in our University Hospital. All consecutive patients undergoing colectomy or proctectomy during this period were analyzed, including those who underwent emergency surgery, had bowel obstruction, or required a stoma.

The start of the inclusion period corresponded to the initiation of the ERAS protocol in our surgical service. Since need for ICU stay in the immediate postoperative period interfered with adherence to the ERAS protocol, this was a criterion for non-inclusion.

The project was submitted to and approved by the local ethics committee.

ERAS protocol

The protocol was developed jointly by the anesthesiology and visceral surgery teams based on an analysis of the scientific literature on the subject and the recommendations of the ERAS® society [8,9] and GRACE group [10]. Table 1 summarizes the different components of the ERAS program observed throughout the study.

Data

Data were collected and recorded systematically in a paper questionnaire and then transferred to an anonymous electronic database. The following information was recorded:

- pre-surgery: weight, height, age, medical and surgical history, American Society of Anesthesiologists (ASA) score, treatments, oral sweetened liquid intake, prescription of pre-medication and surgical indication;
- intraoperative: volume of intravenous fluids administered, body temperature, analgesics administered, antiemetic use, operative time, duration of operation room occupancy, surgical approach, type of anastomosis, drains of the abdominal cavity, stomach and bladder, use of parietal analgesia, and use of bowel preparation;
- postoperative: analgesics administered, anti-emetics administered, course of advancement to oral diet, interval to flatus and stool transit, complications, presence of ileus, interval to ROT, duration of hospitalization.

Morbidity was classified according to the Clavien/Dindo classification [21]. Complications above Grade 2 were considered serious complications.

The interval to global ROT (GROT) was defined as the time from surgery to the time of passage of stool in association with tolerance of solid food intake [14].

Postoperative ileus was defined by the combination of at least two of the following five criteria [13]:

- nausea or vomiting for 12 hours;
- inability to tolerate a solid or semi-solid food for two meals;
- abdominal distension;
- lack of stool or gas for 24 hours;
- radiologic images of ileus on computed tomography (CT) scan.

The ''normal interval'' for GROT was successively redefined as 1, then 2, ... up to 7 postoperative days, and the incidence of ileus was then successively calculated based on these varying definitions.

The theoretical hospital stay corresponded to the date the surgeon authorized hospital discharge while the actual hospital stay corresponded to the date the patient actually left.

The primary endpoint was overall adherence to the ERAS protocol, as measured by the number of protocol measures adhered to during the hospital stay (Table 2).

Statistical analysis

Continuous variables were expressed as medians with interquartile range measurement. A linear regression was performed for variables when a correlation with the time was sought. The evaluation of the significance of the latter was carried out by a search for the correlation factor and the Fisher test.

Thereafter, we arbitrarily chose an 85% compliance rate with the ERAS protocol to be acceptable. Group (M) (with < 85% compliance) was compared to Group (P) (with > 85% compliance) to assess the impact of ERAS on the incidence of prolonged ileus.

For this phase of the study, ''prolonged ileus'' was defined as ileus extending beyond four days. For categorical variables, results were reported as numbers and percentages and compared using Pearson's Chi^2 test. For quantitative variables, results were reported as the median with 25th

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Table 1 Items included in the ERAS protocol and definitions.

Evaluated item	Definition
Preoperative phase	
Information and advice to patient	Performed by the surgeon and anesthesiologist preoperatively
Oral sweetened liquids	Oral administration of 800 mL of sweetened liquids the night before surgery and of 400 mL on the morning of surgery the patient has problems with gastric emptying, bowel obstruction or emergency surgery
Reduction of preoperative fasting	Preoperative fasting is reduced to six hours for solid food and 2 hours for clear liquids
Immunonutrition	Oral administration of 3 packets daily for 7 days before surgery for patients with cancer but without obstruction or emergency presentation
No bowel preparation	No bowel preparation for all colectomies and for proximal proctectomies Bowel preparation for mid and low rectal resections
Intraoperative phase	
Prevention of postoperative nausea	Administration of at least two anti-nausea medications including 8 mg of Dexamethasone at anesthesia induction
Laparoscopic approach	A laparoscopic approach is preferred but this is left to the judgment of the surgeon
Early removal of nasogastric tube	The nasogastric tube is removed at the end of the procedure before the patient awakens, except for patients with preoperative bowel obstruction
Avoidance of operative drainage	Drains are avoided except for specific contexts or for proctectomies
Moderate administration of IV fluids based on at least one hemodynamic criterion	500—1000 cc IV fluid for surgeries lasting < 180 min and 1500 cc if > 180 min
Multimodal analgesia	Combination of systemic analgesia (PCA morphine) and locoregional analgesia (ropivicaine instilled continuously via a multi-perforated catheter)
Prevention of hypothermia	Use of a hot-air warming blanket and IV fluid warmer
Postoperative phase	
Early mobilization	Mobilization: on D0, out of bed; on D1 and D2, out of bed > 8 hrs/day
Early alimentation	Ad libitum water intake in the first six hours postoperatively and upon return to the ASU
Pulmonary physical therapy	Bedside incentive spirometry and pulmonary physiotherapy for 15 min/day on postoperative D1, D2, D3
Restriction of intravenous crystalloids	As soon as oral hydration is resumed, reduce intravenous crystalloids, to 500 mL/day
Early removal of bladder catheter	Removal of Foley catheter on D1 except for mid or low rectal resections or bladder resection
Early removal of intravenous lines	Removal of peripheral IV line by D4
Use of at least one prokinetic intestinal agent	Administration of at least one of the following prokinetic agents: oral magnesium citrate (2 tablets per day) and/or chewing gum (for 15 minutes, 3 times per day)

and 75th percentile, and then compared using the nonparametric Mann-Whitney test.

Associations between the various confounding factors and the presence of prolonged ileus were studied by multivariate logistic regression.

The statistics were calculated using SPSS software 15.0®.

A P-value < 0.05 was considered significant.

Results

During the study period, a total of 131 patients were included, 47 of whom were women (37.9%).

Study population

Indications for surgery were cancer in 76 cases (58%), diverticulosis 30 cases (22.9%), colon polyp in 6 cases (4.6%) and left colon volvulus in 5 cases (3.8%). Other indications were noted in 14 cases (10.7%).

Eleven patients (8.4%) had preoperative bowel obstruction.

Surgery was performed laparoscopically in 68.7% of cases.

The data concerning general characteristics and comorbidities of the study population are reported in Table 3.

Postoperative course

The median interval to passage of flatus was 2 days (1; 2) and 3 days (2; 4) for passage of stool. The median interval to GROT was 3 days (2; 4).

Fig. 1 reports the variation of intervals to GROT in relation to protocol adherence. The interval to GROT, and to ROTF improved significantly with increasing protocol adherence ($P < 0.001$, $r^2 = 0.11$ and $P = 0.04$, $r^2 = 0.03$ respectively).

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Table 2 Compliance with different items of the protocol for each operative phase (131 patients).

Measures in protocol	*n*	%
Preoperative phase	4 (3; 5)[a]	
Information and advice to patient	112	85.5
Reduction of preoperative fasting[b]	84	75.7
Oral sweetened liquids[c]	61	70.9
Immunonutrition[d]	40	58
No bowel preparation	120	91.6
Intraoperative phase	5 (4; 6)[a]	
Prevention of postoperative nausea	66	50.4
Laparoscopic approach	90	68.7
Early removal of nasogastric tube	114	87
Avoidance of operative drainage	103	78.6
Moderate administration of IV fluids based on at least one hemodynamic criterion	82	62.6
Multimodal analgesia	94	71.8
Prevention of hypothermia	131	100
Postoperative phase	5 (4; 6)[a]	
Early mobilization[e]	36	27.5
Early alimentation	106	80.9
Pulmonary physiotherapy	93	71
Restriction of intravenous crystalloids	103	78.6
Early removal of bladder catheter	108	82.4
Early removal of intravenous lines	78	59.5
Use of at least one prokinetic intestinal agent	118	90
Total items: pre-, intra-, postoperative	14 (13; 16)[a]	

[a] Median (1st quartile; 3rd quartile), *n*: number of measures that were complied with.
[b] Denominator = 111 patients (excluding those with obstruction or undergoing emergency surgery).
[c] Denominator = 86 patients (excluding those with poor gastric emptying, emergency surgery, or obstruction).
[d] Denominator = 69 patients (includes patients with cancer, but without emergency surgery, or bowel obstruction).
[e] Data missing in 4 patients.

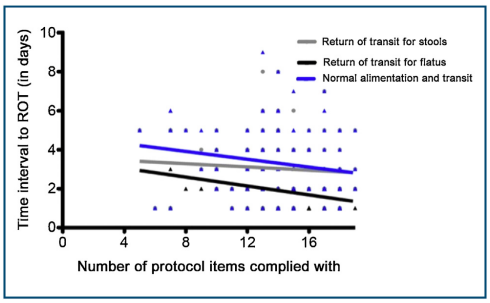

Figure 1. Time interval to ROT as a function of the number of items complied with in the ERAS protocol.

Table 3 General data and co-morbidities of the study population (*n* = 131).

Median age	66 (55–78.5) years
Sex, n (%)	
Male	84 (64.1)
Female	47 (35.9)
ASA score, n (%)	
ASA 1	23 (17.55)
ASA 2	56 (42.74)
ASA 3	47 (35.87)
ASA 4	5 (3.81)
Body Mass Index	25 kg/m^2
Co-morbidity, n (%)	
None	6 (4.6)
Diabetes	15 (11.5)
Hypercholesterolemia	24 (18.3)
Hypertension	33 (25.2)
Atrial fibrillation	7 (5.3)
Obesity	20 (15.3)
Alcohol or substance abuse	11 (8.4)
Smoking	29 (22.1)
Previous gastrointestinal surgery, n (%)	
Laparoscopy	11 (8.4)
Laparotomy	36 (27.5)
Colectomy	8 (6.1)
Medication history, n (%)	
None	30 (23)
Multiple medications > 5	37 (28.2)
Anti-platelet medication	18 (13.7)
Anticoagulant medication	17 (13)
Oral hypoglycemic medication	12 (9.2)
Insulin therapy	7 (5.3)
Preoperative chemotherapy	7 (5.3)

Interval to passage of stool improved but this was not statistically significant ($P = 0.35$).

A nasogastric tube had to be reinserted in 24 cases (18.3%) for a median duration of two days because of feculent vomiting. The indication was always related to fecal vomiting.

Ileus was found in 1.5 to 62.5% of the cases, depending on the cut-off time chosen in the definition of ileus (Table 4).

Overall mortality in our series was 2% (3 deaths).

Table 4 Incidence of ileus based choice of definition (interval to return of transit for stool and toleration of oral feeding).

Definition of ileus	Incidence of ileus, *n* = 131 (%)
Interval > 2 days	82 (62.5)
Interval > 3 days	52 (39.6)
Interval > 4 days	32 (24.4)
Interval > 5 days	13 (9.9)
Interval > 6 days	4 (3)
Interval > 7 days	2 (1.5)

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Table 5 Variation of certain demographic and operative criteria for Groups P and M.

	Group P ≥ 85% compliance ($n = 45$)	Group M < 85% compliance ($n = 86$)	*P*-value
Male sex	27 (60%)	57 (66.3%)	0.48
Surgical indication for cancer	23 (51.1%)	53 (61.6%)	0.25
Obesity	11 (24.4%)	9 (10.5%)	0.04
ASA score			0.16
1	10 (22.2%)	13 (15.2%)	
2	23 (51.1%)	33 (38.4%)	
3	12 (26.7%)	35 (40.7%)	
4	0	5 (5.8%)	
Past surgical history			
Laparotomy	8 (17.8%)	28 (32.6%)	0.07
Laparoscopy	4 (8.9%)	7 (8.1%)	0.883
COPD	0	8 (9.3%)	0.03
Emergency surgery	3 (6.7%)	16 (18.6%)	0.06
Ileo-colic anastomosis	25 (55.6%)	33 (38.4%)	0.06
Ileus	12 (26.7%)	40 (46.5%)	0.03

ASA: American Society of Anesthesiologists.

The overall immediate postoperative morbidity was 46.6% ($n = 61$) while the rate of serious complications was 9.1% ($n = 12$).

The rate of anastomotic leak was 9.9% ($n = 13$) while rectal bleeding occurred in 8.4% ($n = 11$).

The median duration of actual hospital stay was seven days (5; 11) and the median theoretical duration of stay was six days (4; 9) with no significant difference between the two groups ($P = 0.08$).

Association between ileus and ERAS

The median operating time for Group P was 180 min (150; 200) and for Group M it was 180 min (120; 240); there was no significant difference between the two groups ($P = 0.81$). Median age was 69 years (57; 59) for Group M and 61 years (52: 75) for Group P; the difference was not significant ($P = 0.08$).

With regard to qualitative variables (Table 5), there was a statistically significant association between the incidence of ileus and a < 85% adherence to the ERAS protocol ($P = 0.03$).

Differences in characteristics of the two groups with regard to obesity ($P = 0.04$) and chronic obstructive pulmonary disease (COPD) ($P = 0.03$) were statistically significant.

A multivariate analysis adjusted for risk factors for ileus highlighted a significant decrease in ileus when adherence with the ERAS protocol was greater than 85% (OR = 0.35; 95% CI = 0.15 to 0.83). Other factors were not significant (Table 6).

Discussion

In the study period, 131 consecutive patients underwent colon and rectal surgery following an ERAS protocol.

The rate of compliance with the protocol was variable for certain items and was reported between 27.5 and 100%. The study by Ahmed et al. [22] showed that compliance with the protocol varied from study to study but particularly that compliance decreased during the postoperative phase. Compliance was also better when cases were enrolled in a formal protocol [23]. To improve protocol adherence, some authors recommend the creation of specialized units and task forces to train medical and paramedical teams, with participation in internal audits to identify items that are prone to non-compliance [6,22,24,25]. In our series, the only item where compliance fell below 50% was early mobilization. This is essentially due to ingrained habits of the nursing staff. However, in our experience, we have observed an improvement in compliance over time.

The ileus rate reported by our team ranged from 1.5 to 62.5% depending on the choice of cut-off interval. The incidence of ileus reported in the literature is between 10 and 30% [1,15–20]. However, the definition of ileus, the cut-off time to GROT, and the endpoint chosen to define GROT are very variable among the authors, with cut-off variably defined as 3 to 7 days [1,15–20].

Our reported rate of ileus is comparable to those in the literature, but confirms the great variability in the reported incidence of ileus as defined within the same series.

Table 6 Multivariate analysis of factors potentially associated with ileus.

	Odds ratio	Confidence interval	*P*-value
Protocol compliance > 85%	0.35	0.15–0.83	0.02
Male sex	1.15	0.53–2.48	0.72
Obesity	0.71	0.24–2.15	0.57
COPD	0.61	0.12–2.91	0.53
Ileo-colic anastomosis	1.54	0.73–3.26	0.25
Emergency surgery	0.48	0.16–1.4	0.18

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Most studies of ileus and its risk factors are therefore not comparable.

Furthermore, it has now been clearly shown that ERAS enables a reduction in duration of hospital stay and postoperative morbidity [6,7,11,12,26]. However, the impact on GROT is difficult to assess because of the above-mentioned bias in the definitions of ileus.

The interval to passage of stool is an objective indicator and not subject to an assessment bias. Thus, our study showed that as compliance with the ERAS protocol increased, there was a significant decrease in the interval to MTPF and GROT.

By itself, the reduction in interval to passage of stool in relation to protocol compliance is not significant. However, the reduction of this duration is evident in Fig. 1. The lack of significance can probably be explained by the fact that several practitioners chose not to order the use of oral laxatives that were recommended in the protocol. This could therefore bias the interpretation of this result.

To confirm the usefulness of ERAS in preventing prolonged ileus, comparison of the two groups showed a significant association between a $\geq$ 85% compliance rate and a low rate of ileus ($P = 0.03$). However, in univariate analysis, there was a difference of distribution of COPD patients ($P = 0.03$) and obese patients ($P = 0.04$). These two factors are known to be risk factors for ileus [15,17,18,27].

In multivariate analysis, a $\geq$ 85% compliance rate was protective against the risk of postoperative ileus (OR = 0.35 [95% CI = 0.15 to 0.83]; $P = 0.02$). No other factors were statistically significant. This difference from other published results probably arises from the variability in the definition of ileus in different articles [15,17—20].

However, since there is no consensual definition, we used a definition drawn from a literature review and comprehensive investigation [13]. This definition seems to be increasingly employed in recent studies [16].

Despite this definition bias that is present in all studies on ileus in the literature, this study is, to our knowledge, the first to specifically examine the relationship between ileus and ERAS and stresses the need to clearly delineate a consensual definition of ileus. These results should provide an evidence-based approach for the establishment of models for the management of postoperative ileus.

Conclusion

In our study, compliance with an ERAS protocol improved recovery of intestinal motility with a decreased interval to passage of flatus, passage of stool, and tolerance of oral alimentation of solids. The direct consequence of strong adherence to the protocol is a reduced risk of postoperative ileus.

However, within the same series, the results of the incidence of postoperative ileus are not reproducible depending on the definition of ileus. This points to a problem of reproducibility involving all studies on this subject and therefore the need for a clear and agreed definition of ileus, thereby allowing comparability among the different studies.

Disclosure of interest

The authors declare that they have no competing interest.

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Les résultats de **l'article 3** nous permettent de conclure que la reprise du transit est largement améliorée par la réhabilitation améliorée. Toutefois, la définition de l'iléus postopératoire reste un biais majeur dans la reproductibilité des études en raison d'une variabilité majeur des cut-off permettant de parler d'iléus postopératoire. Nous avons donc proposé une classification qui ne serait pas basée sur un délai de reprise du transit mais sur les conséquences de l'apparition d'un iléus postopératoire.

D. Article 4 publié dans l'International Journal of Colorectal Diseases

RESUME

But : il n'y a pas, dans la littérature, de définition consensuelle de l'IPO. Ceci mène à un manque de reproductibilité entre les études. Les buts de cette étude étaient (i) de proposer et d'évaluer une classification de l'iléus postopératoire basée sur ses conséquences et (ii) d'évaluer la reproductibilité de cette classification.

Méthodes : une enquête nationale était menée en suivant le modèle du DELPHI, afin de créer une classification de l'iléus primaire. Cette classification a ensuite été évaluée sur une cohorte de patients qui ont eu une chirurgie colorectale, puis la reproductibilité a été évaluée dans 5 hôpitaux universitaires parmi des chirurgiens juniors et des séniors.

Résultats : Une classification en 5 grades a été proposée, du grade A (moins important) à grade E (décès). Pour une meilleure différenciation, le grade D a été séparé en 2 catégories (D1/D2).

Au total, 173 patients ont été inclus pour valider la table. Quarante ont eu un iléus (23.1%). Le grade A avait lieu dans 10 cas, le grade B dans 10 cas, le grade C dans 14 cas, le grade D1 dans 2 cas et le grade D2 dans 2 cas. Les décès en lien avec un IPO (grade E) étaient rapportés dans 2 cas. Les patients avec un IPO grade A récupéraient leur transit plus rapidement que les autres (p=0.01) et avaient plutôt été opérés par coelioscopie (p=0.04).

Par ailleurs, en ce qui concerne la reproductibilité, le coefficient de corrélation intraclasse (CCI) était de 0.83 dans la population générale, et de 0.83 et 0.82 respectivement dans la population de juniors et de séniors.

Conclusion : Cette classification est facile à utiliser et à reproduire. Elle devrait améliorer la reproductibilité et l'évaluation des IPO mais cette étude préliminaire doit être confirmée dans une étude internationale multicentrique de plus grande ampleur.

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ORIGINAL ARTICLE

Proposal of a new classification of postoperative ileus based on its clinical impact—results of a global survey and preliminary evaluation in colorectal surgery

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Abstract
Purpose There is no consensual definition of postoperative ileus (POI), which leads to a lack of reproducibility. The aims of this study were (i) to propose and evaluate a classification of postoperative ileus based on its consequences and (ii) to assess the reproducibility of the classification.
Methods A national global survey was carried out according to the DELPHI method in order to create a classification of primary POI. The classification was subsequently tested on a cohort of patients who underwent colorectal surgery. Finally, a reproducibility test was performed in five teaching hospitals with junior and senior surgeons.
Results A five-stage classification was proposed: grade A (least) to grade E (worst). For better differentiation, subcategories (D1/D2) were included. Overall, 173 patients were included who underwent colorectal surgery. Forty of them experienced primary postoperative ileus (23.1%). Grade A occurred in 10 cases, grade B in 10 cases, grade C in 14 cases, grade D1 in 2 cases, and grade D2 in 2 cases. POI-related death (grade E) occurred in 2 cases. Patients with grade A POI recovered their gastrointestinal function significantly faster than those with higher grades ($p = 0.01$), and were more likely to undergo laparoscopic surgery ($p = 0.04$). The Intraclass Correlation Coefficient (ICC) was 0.83 in the overall population, and 0.83 and 0.82 respectively in the junior and senior surgeon populations.
Conclusion This classification is easy to both use and reproduce. It will improve the reproducibility, evaluation, and assessment of POI. These preliminary results should be confirmed in a multi-centric international study.

Keywords Postoperative ileus · Classification · Postoperative morbidity

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Background

In 2005, Kehlet et al. concluded that a clear definition of postoperative ileus (POI) was required [1]. Ten years later, the need for a consensual definition still exists, especially with regard to the cutoff point for normal POI [2]. Nevertheless, literature has become more homogenous since the definition proposed by Vather et al. in 2013 [3] and the confirmation of the endpoints by Van Bree et al. in 2014 [4]. However, there is a lack of agreement about the cutoff point for normal or prolonged POI. Postoperative ileus is reported to occur in 3–32% of cases in overall surgery [2, 5–10]. However, cutoff points vary between 3 and 7 days [3, 5–9], inevitably changing the POI rate within the same population [11]. This leads to non-reproducibility of studies. The hope to answer this

question of delay is probably futile. Indeed, knowledge of physiopathology is limited and unlikely to provide answers due to inter-individual variability. Vagal activation is one of the pathways that resolve POI [12]. The pathogenesis of POI is explained by a reactive inflammation after intestinal manipulation [13]. First effects occur within 3 h after operation. However, the delay before vagal activation and the pathway leading to vagal activation are not known.

Definitions from Vather et al. [3] and Van Bree et al. [4] are meaningful in clinical practice because they help with the diagnosis of POI. However, in case of clinical studies, these definitions remain insufficient due to the lack of consensus regarding the normal delay to the recovery of gastrointestinal functions. Drawing on the model of the Clavien-Dindo classification [14], POI has several consequences that could be used to put forward a classification that would be meaningful in clinical studies and could ensure better reproducibility between works. Indeed, PPOI (prolonged postoperative ileus) increases not only the length of hospital stay but also the management costs [15], the risk of severe complications, and the need for further surgery [16]. Consequences of POI include vomiting, which can lead to pulmonary aspiration [17]. POI also causes impaired fluid, electrolyte and nutrient reabsorption, fluid and electrolyte imbalance, and nutritional deficiencies [17].

When postoperative ileus is due to an external cause of the bowel, POI is classed as a secondary ileus. It differs from primary POI in that it does not respond to the same physiopathology. Secondary POI is the consequence of an adverse effect of surgery [15], whereas primary POI is an autonomous paralysis of the smooth muscle of the bowel that has its own consequences. Given this difference in physiopathology, primary POI should have its own specific classification that excludes secondary POI.

The main aim of this work was to propose a new classification of primary POI based on its consequences and the possibility to use it in clinical and experimental studies. Additional goals were to evaluate the classification in a preliminary study that included a cohort of patients undergoing colorectal surgery and to assess its reproducibility through a national survey.

Materials and methods

All steps are summarized in Fig. 1.

Proposal of a classification—National DELPHI survey

A work group of surgeons and anesthetists involved in early rehabilitation was created. Twenty-two contributors from France, Belgium, and Switzerland participated in the survey. They were all employed in high-volume centers and were involved in improving the postoperative course. The method used to create the classification was the DELPHI method [18].

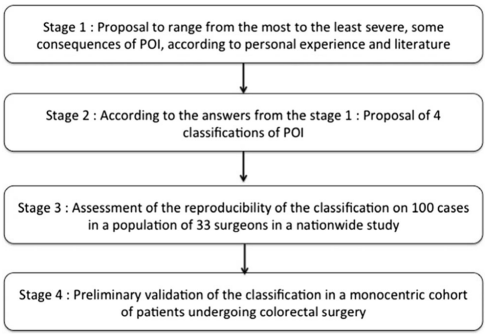

Fig. 1 Flowchart of the different stages of the classification proposal

Contributors were contacted by e-mail. The first e-mail asked participants to classify, from most severe to least severe, the different consequences of POI. A space was left free to allow participants to suggest other items. The survey was performed using the website SurveyMonkey®. The items and results of the first stage of this work are reported in Fig. 2. The results of the survey are noted according to the valorization of the website (number of citations, range of citations, etc.).

The items were proposed according to literature and the personal experience of the investigators. If participants did not answer the e-mail, a reminder was sent 2 weeks later to request an answer.

For the second stage of this work, four classifications were proposed according to the answers received. A new e-mail was sent to the participants. They were asked to select the classification that was, in their opinion, best adapted for POI. Sixteen contributors responded.

Forty-five percent of the contributors agreed on the same classification. The classification was subsequently adapted to suit all the contributors.

Validation of the classification

The classification was assessed on a cohort of 173 consecutive patients who underwent colorectal surgery between 1 June 2012 and 1 July 2014 in a single tertiary center. Data was retrospectively extracted from a prospective database, collected with the aim of performing an audit of enhanced recovery protocols. All consecutive patients who underwent emergency surgery or laparotomy were also included. Some of these patients were included in a previous study in which we demonstrated that enhanced recovery programs can reduce POI [11].

In this monocentric cohort, patients who required intensive care following surgery were not included as they were unable to follow the early rehabilitation protocol.

Information regarding the perioperative course was collected in an anonymized electronic database and related to the postoperative course: occurrence of POI, need for prokinetics,

Type 1 error was set at 0.05. Statistics were completed using the program Statistical Package for the Social Sciences (SPSS version 10.0. Chicago, IL). The value $p < 0.05$ was considered statistically significant.

Results

Proposal of a classification

After 2 months, the DELPHI survey was completed, and the following classification was put forward and accepted by most participants. This classification concerned all adverse effects exclusively relating to POI.

- Grade A: no consequence of POI apart from an increase in the length of stay.
- Grade B: need for symptomatic measures or diagnostic examinations (such as laxatives, prokinetic drugs, antispasmodic drugs, antiemetic drugs, need for decreased regimen, or need for vein access, etc.).
- Grade C: need for nasogastric tube intake or hospital readmission after discharge.
- In the event where the nasogastric tube is not removed immediately, grade C should only be considered if the nasogastric tube was removed before it required replacement.
- Grade D: severe consequences of POI.

- D1: general complications (such as ionic imbalance, pneumopathy, auricular fibrillation, etc.)
- D2: need for intensive care unit or further surgery.

- Grade E: death.

Assessment of the reproducibility

The ICC index was 0.82 in the overall population (CI95% 0.77–0.86).

In the junior surgeon population, the ICC index was 0.82 (CI95% 0.78–0.86), whereas it was 0.81 (CI95% 0.77–0.85) in the senior surgeon population.

Validation of the classification

Among the 173 patients included, ileus occurred in 50 patients (28.9%). Ten patients experienced secondary ileus due to anastomotic leakage or hemoperitoneum.

Forty patients experienced primary ileus (23.1%). The classification was tested exclusively on primary POI. Grade A occurred in 10 cases (25%), grade B in 10 cases (25%), grade C in 14 cases (35%), grade D1 in 2 cases (5%), grade D2 in 2 cases (5%), and grade E in 2 cases (5%).

Median delay to first flatus was 3 days (2; 3) and median delay to first stool was 4 days (4; 5) in the overall population. Median length of stay was 9 days (7; 12).

According to this classification, laparoscopy was associated with a smaller grade of POI (grade A; $p = 0.04$) (Table 1). Conversely, a higher ASA score was associated with a higher rate of high-grade POI ($p = 0.049$ and $p = 0.01$).

Time to recovery of gastrointestinal motility (solid food tolerance + stool) was not correlated with the grade of our classification of POI ($r^2 = 0.01$; $p = 0.54$) in linear regression, but POI grade A had a significantly faster recovery of gastrointestinal motility ($p = 0.01$).

Discussion

Although there is now a definition for POI, the absence of a consensus regarding the cutoff point for normal POI within the surgical community leads to a lack of reproducibility of clinical studies. A classification based on objective consequences of POI could make studies on POI reliable. Indeed, in five recent studies analyzing risk factors for POI, four different cutoff points for POI were used [5–7, 9, 19]. In these studies, the risk factors and the POI rate were different. Some studies considered that patients suffered from ileus if they required a nasogastric tube [20]. The proposed classification showed that, in our series, only 14 patients (35%) required a nasogastric tube, which highlights the need for a consensual classification based on consequences.

Various factors, such as constipation, influence the time to bowel motility recovery, which leads to a possible misinterpretation of these factors as risk factors for POI [21]. As such, we believe that a classification of POI should be based on consequences rather than delay. The definition of PPOI proposed by Vather et al. is clear [3] and should be extended to all POI, without including the notion of delay. Indeed, in our experience, some patients treated through early recovery protocols did not experience gastrointestinal blockade. That is why we think that considering POI from the first day could ensure better reproducibility of POI incidence between studies. In addition, the delay is too random. Despite knowledge of some classifiers in the series of events that lead to POI and its resolution, none of the classifiers make it possible to predict the duration of normal POI.

Interestingly, in our cohort, the grades of this classification were not correlated with the duration of POI. However, known risk factors of ileus, such as respiratory comorbidities or preoperatory sepsis (which increase the ASA score) [5, 6], were associated with high POI severity, while laparoscopy was associated with a lower grade of POI severity. Laparoscopy is known to be protective against POI [7].

Table 1 Association between the grade of POI and some of the different recognized factors of POI in literature

	Grade A			Grade B			Grade C		
	Yes $n = 10$	No $n = 30$	p value	Yes $n = 10$	No $n = 30$	p value	Yes $n = 14$	No $n = 26$	p value
Gender, male	6 (60%)	19 (63.3%)	>0.9	4 (40%)	21 (70%)	0.13	12 (46.2%)	14 (53.8%)	0.12
Age, years	55 (68;75)	80 (67;85)	0.06	82 (56;88)	81 (67;85)	0.38	73 (67;87)	3 (2;3)	0.57
BMI, kg/m^2	26 (20;28)	23 (24;27)	0.68	26 (20;28)	24.5 (23;27)	0.31	25.5 (24;27)	24 (22;27)	0.17
Duration of surgical procedure	180 (180;240)	150 (120;210)	0.25	180 (180;240)	150 (120;210)	0.34	165 (145;250)	180 (120;213)	0.48
Laparoscopy	6 (60%)	6 (20%)	0.04	1 (10%)	11 (36.7%)	0.23	4 (40%)	8 (66.7%)	>0.9
Manual anastomosis	6 (60%)	18 (60%)	>0.9	8 (80%)	16 (53.3%)	0.26	6 (60%)	18 (69.2%)	0.18
Ostomy	0	1 (3.3%)	>0.9	0	1 (3.3%)	>0.9	0	1 (7.1%)	0.35
ASA score			0.37			0.049			0.014
ASA 1	1 (10%)	2 (6.7%)		1 (10%)	2 (6.7%)		1 (7.1%)	2 (7.7%)	
ASA 2	6 (60%)	10 (33.3%)		6 (60%)	10 (33.3%)		2 (14.3%)	14 (53.8%)	
ASA 3	3 (30%)	15 (50%)		1 (10%)	17 (56.7%)		11 (78.6%)	7 (26.9%)	
ASA 4	0	3 (10%)		2 (20%)	1 (3.3%)		0	3 (11.5%)	
Emergency surgery	0	4 (13.3%)	0.55	2 (20%)	2 (6.7%)	0.22	1 (7.1%)	3 (11.5%)	>0.9
Indication for colonic obstruction	0	5 (16.7%)	0.31	2 (20%)	3 (10%)	0.58	1 (7.1%)	4 (15.4%)	0.64
Corticotherapy	1 (10%)	1 (3.3%)	0.40	0	2 (6.7%)	>0.9	1 (3.8%)	1 (3.8%)	>0.9
Preoperative irradiation	0	1 (3.3%)	>0.9	0	1 (3.3%)	>0.9	1 (7.1%)	0	0.35
Right colectomy	5 (50%)	17 (56.7%)	0.73	7 (70%)	15 (50%)	0.46	7 (50%)	15 (57.7%)	0.64
Length of stay, days	7 (5;8)	10 (8;14)	<0.01	10 (6;12)	9 (8;12)	0.75	10 (9;14)	8 (6;10)	0.03
Time to GI motility recovery, days	4 (4;4)	5 (4.25;6)	0.01	5 (4.25;5.75)	5 (4;5)	0.31	5 (5;6)	4.5 (4;5)	0.13
Time to first flatus, days	4 (4;4)	4 (3;5)	0.30	5 (4.25;5.75)	4 (3;5)	0.99	4 (3;5)	4 (4;5)	0.29
Time to first stool, days	3 (2;3)	3 (2;4)	0.82	3 (3;3)	3 (2;4)	0.01	3.5 (2;4)	3 (2;3)	0.36

Another interesting result was that while time to GI motility recovery was significantly different between grade A POI and the other grades ($p = 0.01$), there was no significant correlation between POI duration and POI grade according to our classification. In addition, there was a significant difference in the length of hospital stay between grade A POI and the other grades ($p < 0.01$). These results are promising and could lead to better management of POI. However, they should be confirmed in a larger prospective cohort.

Apart from simply classifying POI, another benefit of this classification proposal is the possibility to compare the effectiveness of early rehabilitation protocols in reducing complications that result directly from POI. The effect of protocols on bowel motility remains uncertain, but they seem to improve the delay to bowel motility recovery [22–24]. In addition, there is no information about the reduction of complicated POI. Arguably, in terms of cost-effectiveness and well-being, reducing severe complications of POI is more important for patients and society, rather than gaining 1 day of delay to gas recovery. The proposed classification would make it possible to assess early rehabilitations protocols.

Finally, the reproducibility of the proposed classification was assessed in a population of 33 surgeons (17 senior surgeons and 16 junior surgeons) and the overall ICC index was 0.85. Literature and statistical analyzers consider this result as indicative of good reproducibility [25].

It is likely that this result is underestimated, given that surgeons assessed 101 cases of patients with POI at the same time, which may have resulted in a lack of concentration towards the end of the test.

In addition, another factor resulting in a decrease of the ICC index was the confusion surrounding the Clavien-Dindo classification [14]. Several surgeons classed deaths caused by general complications as POI-related. To improve understanding of the classification and ensure better reproducibility, the classification has been made more detailed in the final version above. Any confusion should disappear with experience and use, and should be assessed further.

As a general rule, data is usually collected by junior surgeons, which is why they were specifically included in this work, which is aimed at assessing reproducibility. Junior surgeons found reproducibility to be good and the ICC index was 0.82. This result was the same as that of senior surgeons, which support the argument that the proposed classification is easy to use.

The classification's potential limitations are the same as those of the Clavien-Dindo classification [14]. The classification can mainly be used for clinical or experimental studies; it has a low significance in usual practice given that it does not lead to a change in management. However, better reproducibility between studies will lead to a better understanding of pathways that lead to POI according to the severity of its consequences. A better understanding of POI will, in turn, lead to better management in clinical practice.

Limitations also include subjectivity of the management and subjectivity of the interpretation. However, reproducibility between multiple teams of surgeons with different levels of training and habits was acceptable and comparable with the one displayed by Dindo et al. [14], who reported an 87–91% accuracy rate at the beginning of their experiment. Moreover, this classification reflects the management of POI and could allow for a better comparison and understanding of management between teams. In fact, management is subjective but the classification is objective, based on the reality of management.

We have shown that the proposed classification is easy to use by any surgeon of any level. It could be the first stage before the acceptance of a consensual classification of POI, which would lead to a better comprehension of this frequent postsurgical complication and, subsequently, to more effective management in clinical practice.

Conclusion

The proposal of a POI classification based on its consequences is the result of the French national survey DELPHI. The classification is easy to use and reproduce by both junior and senior surgeons. A general use of this classification in literature on POI will improve the reproducibility and evaluation of POI between different studies. Given that the classification was validated by a preliminary study on a cohort of patients who underwent colorectal surgery only, an international multicentric study should confirm these results among the whole postoperative course of every surgery.

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This list is unfortunately incomplete but a part of the survey was anonymous to avoid bias. The authors would also like to acknowledge the participants who did not give their name.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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L'article 3 nous a donc permis de proposer une nouvelle classification des IPO afin d'uniformiser et de rendre reproductibles les études cliniques sur le sujet, et les résultats de **l'article 1 et 2** nous ont permis de confirmer la faisabilité de la RA dans des situations précaires. Toutefois, malgré l'amélioration des fonctions GI par le biais des programmes de RA, l'iléus postopératoire demeure fréquent (entre 20 et 70% selon la définition). Nous proposons donc une étude visant à rechercher des biomarqueurs de l'IPO dans la paroi colique, mais aussi l'impact des médiateurs lipidiques dans l'IPO au sein de la RA afin de proposer de nouvelles voies thérapeutiques ou prophylactiques de l'iléus.

E. Article 5 accepté pour publication dans le World Journal of Surgery

RESUME

Introduction : L'IPO reste persistant dans 20-30% des cas de résection colorectale malgré la généralisation de la RA. COX-2 a été identifiée comme une enzyme clé dans l'IPO mais d'autres enzymes de la voie de l'AA ont reçu moins d'attention malgré leur potentiel à être une cible thérapeutique sélective pour prévenir l'IPO. L'objectif était de comparer l'expression des enzymes de la voie de l'AA (i) entre les patients ayant eu une résection colorectale pour tumeur et ayant suivi (ERP) ou non (NERP) un programme de RA, (ii) entre les patients ayant suivi la RA mais ayant eu un IPO (POI) ou non (NPOI), et (iii) de déterminer la capacité des antagonistes de cette voie à moduler l'activité contractile du muscle colique.

Matériel et méthodes : Il s'agit d'une étude translationnelle. Les critères de jugement principal étaient la récupération d'un transit gastro-intestinal, la quantification de l'*ARNm* des enzymes clés de la voie de l'AA (RT-qPCR), les valeurs de contraction *ex-vivo* du muscle lisse colique circulaire. Vingt-huit patients étaient inclus prospectivement dans le groupe ERP et comparés à 11 patients inclus rétrospectivement dans le groupe NERP. Tous ont eu une résection colo-rectale.

Résultats : La RA réduisait significativement l'expression de l'*ARNm* de la COX-2, mPGES1 et HPGDS dans la muqueuse colique. L'expression de l'*ARNm* de mPGES1 et HPGDS était significativement associée à la compliance de la RA (respectivement R^2=0.25, p=0.002 et R^2=0.6, p<0.001). Dans *la muscularis propria*, l'expression de l'ARNm de HPGDS était corrélée avec le délai de récupération d'une motricité gastro-intestinale (p=0.002). Enfin, l'inhibition pharmacologique de mPGES1 augmentait la contraction spontanée ex-vivo du muscle circulaire lisse colique (p=0.03).

Conclusion : Les effets de la RA sur la récupération de la motricité gastro-intestinale sont corrélés avec la compliance à la RA et pourraient emprunter, en partie, la voie de la mPGES1, HPGDS et COX-2. De plus, mPGES1 représente une cible thérapeutique prometteuse afin de réduire l'incidence de l'IPO au sein des patients suivant une RA.

Original article to be submitted to World Journal of Surgery

Anti-inflammatory effects of enhanced recovery programs in early stage colorectal cancer surgery.

Short running title: postoperative ileus and inflammation

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Key Words: Postoperative ileus, mPGES1, arachidonic acid metabolism, COX-2, enhanced recovery programs, colorectal surgery, gastrointestinal functions

Conflict of interest :

Aurélien Venara has been invited to clinical congresses by Nestlé.

Emilie Duchalais, Anne Dariel, Philippe Aubert, Tony Durand, Guillaume Meurette, Malvyne Rolli-Derkinderen, Antoine Hamy and Michel Neunlist declare no conflict of interest in relation with the present manuscript.

Authors' contribution:

Aurélien Venara: conception, design, analysis and interpretation of data, manuscript author, provided criticism of the manuscript, drafted the article and revised it critically for important intellectual content. Final approval of the version to be published

Emilie Duchalais: Data collection, experimentation, provided criticism of the manuscript, drafted the article. Final approval of the version to be published

Anne Dariel: Data collection, experimentation, provided criticism of the manuscript, drafted the article. Final approval of the version to be published

Philippe Aubert: Experimentation, provided criticism of the manuscript, drafted the article. Final approval of the version to be published

Tony Durand: Experimentation, provided criticism of the manuscript, drafted the article. Final approval of the version to be published

Guillaume Meurette: Drafted the article and revised it critically for important intellectual

content. Final approval of the version to be published

Malvyne Rolli-Derkinderen: Drafted the article and revised it critically for important intellectual content. Final approval of the version to be published

Antoine Hamy: Conception, design, analysis and interpretation of data, manuscript author, provided criticism of the manuscript, drafted the article and revised it critically for important intellectual content. Final approval of the version to be published

Michel Neunlist: Conception, design, analysis and interpretation of data, manuscript author, provided criticism of the manuscript, drafted the article and revised it critically for important intellectual content. Final approval of the version to be published

ABSTRACT:

Background: Postoperative ileus (POI) remains persistant in 20-30% of patients, despite the genrealisation of enhanced recovery programs (ERPs). Cyclooxygenase (COX)-2 is identified as a key enzyme in POI but other Arachidonic acide pathway enzymes have received little attention despite their potential as selective targets to prevent POI. The Objectives were to compare the expression of arachidonic acid metabolism (AAM) enzymes (i) between patients who underwent colorectal resection for tumor and followed an ERP or not (NERP), (ii) and between ERP-patients who experimented POI or not and (iii) to determine the ability of antagonists of these pathways to modulate contractile activity of colonic muscle.

Methods: This was a translational study. Main outcome measures were gastrointestinal motility recovery data, *mRNA* expressions of key enzymes involved in AAM (RT-qPCR), ex vivo motility values of the circular colon muscle. Twenty-eight prospectively-included ERP patients were compared to eleven retrospectively-included NERP patients that underwent colorectal resection for tumor.

Results: ERP reduced colonic mucosal COX-2, microsomal prostaglandin E synthase (mPGES1) and hematopoietic-prostaglandin D-synthase (HPGDS) *mRNA* expression. mPGES1 and HPGDS *mRNA* expression were significantly associated with ERP compliance (respectively r2=0.25,p=0.002 and r2=0.6,p<0.001). In *muscularis propria*, HPGDS *mRNA* expression was correlated with GI motility recovery (p=0.002). The pharmacological inhibition of mPGES1 increased spontaneous *ex vivo* contractile activity in circular muscle (p=0.03).

Conclusion:The effects of ERP on GI recovery are correlated with the compliance of ERP and could be mediated at least in part by mPGES1, HPGDS and COX-2. Furthermore, mPGES1 shows promise as a therapeutic target to further reduce POI duration among ERP patients.

Introduction

Postoperative ileus (POI) has a significant effect on patient well-being and furthermore increases morbidity and length of stay [1,2]. The cost of hospitalization for patients with POI is twice that of patients without POI [2], attaining $750 million annually in the US [1,3]. A range of preventive and/or therapeutic strategies has been proposed to reduce the duration of POI. These include pharmacological intervention (prokinetics and/or anti-inflammatory agents) [4-6], vagal stimulation [7] via mastication [8,9] and early feeding programs [10,11]. Enhanced recovery programs (ERPs), recently proposed by the ERAS Society [12,13], organize most of these strategies into a perioperative protocol. ERPs have been shown to improve the postoperative course considerably, reduce length of stay and decrease morbidity [14]. Furthermore, they reduce the duration and occurrence of POI itself [15,16]. However, between 20 and 30% of patients who undergo colorectal surgery will still have POI four days after the intervention, despite the use of ERPs [15]. Therefore, reducing the duration of POI is aimed at improving postoperative outcomes, reducing hospitalization and enabling safe outpatient management after colectomies. Research teams have looked at approaches such as nicotinic chewing gums to improve vagal stimulation [17,18] or prokinetic drugs [19] to make ERPs more effective, but their results fell short of therapeutic expectations. Consequently, POI remains an issue in medical care.

POI affects the entire gastrointestinal tract [20], but most of the strategies described above and most studies in the literature target the small bowel, especially by activating vagal pathways. Indeed, the density of parasympathetic innervation decreases along a rostrocaudal gradient to become low (to inexistent) in the distal bowel [21], which means that these strategies most likely have only a limited effect on the colon. As a result, other strategies targeting colonic activity specifically are necessary to improve POI management and prevention. As previously shown by Schwarz et al., selective small bowel manipulation leads

to pan-digestive inflammation [20] via cyclooxygenase (COX)-2. As such, targeting the arachidonic acid (AA) pathway may be of interest.

AA metabolism [22,24] leads to the synthesis of prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), prostacyclin (PGI2) and thromboxanes via COX-1 and -2. COX-2 has been shown to play a key role in POI, inducing the synthesis of PGD2 and PGE2 in rodents and humans; on the one hand, surgical manipulation increases COX-2 expression [22], on the other hand, COX-2 inhibition (pharmacological or genetic) reduces the duration of surgically-induced POI [25]. PGE2 and PGD2 are lipid mediators produced by the activation of COX-2 pathways *via* microsomal prostaglandin E synthase (mPGES1) and hematopoietic prostaglandin D synthase (HPGDS) or lipocalin-type prostaglandin D synthase (LPGDS), respectively. Increasingly, PGE2 appears to be involved in POI. Animal studies have shown that PGE2 reduces motility via activation of EP2 and EP4 receptors [26,27] and that its concentration increases as a result of surgery [28]. Concerning PGD2, its functional effects on GI motility remain controversial given that it increases contractile activity in rat colon [29] and reduces sensitivity to pressure-induced peristalsis in guinea pigs [30]. However, the impact of POI on mPGES1 or HPGDS expression and their involvement are currently unknown, especially in humans.

The aim of this study was to compare the expression of arachidonic acid metabolism (AAM) enzymes (i) between patients who underwent colorectal tumor resection and followed an ERP or not (NERP), (ii) between ERP-patients who experienced or did not experience POI and (iii) to determine the ability of antagonists of these pathways to modulate the contractile activity of the colonic muscle in order to propose new therapeutics to improve ERP, from bench to bedside.

Materials and Methods

Patients

Twenty-eight patients who underwent colorectal surgery for endoscopically unresectable cancer or polyp in a single center between January 2015 and January 2016 and who followed a perioperative ERP were enrolled in the ERP group. These patients were retrospectively selected so that we could create 2 comparable groups of patients: One that experienced POI and the other that did not.

Criteria for non-inclusion were:

- medical history of esophageal or gastric surgery;
- treatments modifying the metabolism of acetylcholine;
- indication for enterostomy;
- postoperative general complications potentially associated with postoperative ileus, such as septic shock or anastomotic leakage.

Data for the ERP group were prospectively collected from an anonymized database. We note that some of these patients were included in a previous study in which we concluded that ERPs influence POI [15]. The ERP followed in our center is described in this essay [15]. None of the above-mentioned patients underwent preoperative chemotherapy.

The ERP group was compared to a historical cohort of 11 patients who underwent colorectal tumor resection, but did not follow an ERP (NERP). This historical cohort came from the biobank of another center in which ERP was not implemented at the moment of tissue collection. Data for the NERP group were collected retrospectively. Differences between ERP and NERP management (pre and per-operative) are reported in table 1.

None of the patients included in this essay received pre-, peri- or postoperative Non-Steroidal Anti-Inflammatory drugs (NSAIDs).

Data collected for the two groups were:

(i) Patient characteristics: gender, medical history, surgical history, treatment;

(ii) Operative data: surgical access, anesthesia, intervention, type of anastomosis;

(iii) Postoperative data: delay to first flatus, delay to first stool, delay to GI motility recovery, postoperative morbidity, POI occurrence, length of stay, compliance to ERP;

(iv) Cancer information: Dukes Stage.

Definitions of clinical outcomes

GI functions were assessed using the delays to first flatus, first stool and GI motility recovery. Delay to GI motility recovery was defined using the endpoint described by Van Bree et al. [31]. Motility was considered as recovered when patients had stools and tolerated solid food [32].

POI was defined as per Vather et al. [32] and diagnosed when two or more of the following symptoms were present after 4 days:

- nausea or vomiting in the preceding 12 hours;
- inability to tolerate a solid or semisolid oral diet for the preceding two meals;
- abdominal distension;
- absence of flatus and stool in the preceding 24 hours;
- radiological evidence of ileus on plain abdominal radiography or abdominal computed tomography in the preceding 24 hours.

Biobanks

Tissues from the patients who followed the ERP were stored in the biobank of the Biological Resources Center of Angers (BB-0033-00038) and registered under the number CB-2011-05. Tissues from the historical cohort were stored in the biobank of IMAD (*Institut des maladies de l'appareil digestif*, the Institute for Diseases of the Digestive System) and registered under number DC-2008-402. Concerning the historical cohort, only mucosa/submucosa samples were available for this study. Both biobanks were approved by the French Ministry of Science and Research. All patients gave their informed and written consent for the study.

Tissue conditioning

Tissue fragments (~1cm X 1cm) were collected from the proximal (left colectomy) or distal (right colectomy) extremity of the resected colon away from the tumor in a macroscopically normal area. Fragments of mucosa/submucosa and muscularis propria/serosa were macroscopically separated. To simplify the manuscript, the first fragment will be called mucosa and the second one will be called muscularis propria in the results.
Fragments from the ERP group were stored in liquid nitrogen at -80°C. The delay to congelation ranged from 30 to 45 minutes.

Quantitative polymerase chain reaction (qPCR) analysis

Total RNA was extracted from the samples (mucosa/submucosa and muscularis propria/serosa), using Nucleospin RNA II (Macherey-Nagel, Hoerdt, France). cDNA were synthetized using Superscript III Reverse Transcriptase (Thermo Fisher Scientific, Courtaboeuf, France) according to the manufacturer's recommendations. Real-time PCR were

performed using the Fast Sybr Green Master Mix kit (Applied Biosystems, California, USA) and run on a StepOnePlus thermocycler (Applied Biosystems, California, USA).

Each qPCR reaction product was directly loaded onto non-denaturing 2% agarose gel and visualized under UV transillumination. Specificity of the primers was determined by sequencing the PCR products. Genes studied were cyclooxygenase 1 and 2 (COX-1 and -2), microsomal prostaglandin E synthase (mPGES1), hematopoietic prostaglandin D synthase (HPGDS) and lipocalin-type prostaglandin D synthase (LPGDS).

Primer sequences were:

- homo sapiens, COX-1 (NM_000962.2) Fw: 5' TCCTGTTGGTGGACTATGG 3'
  Rev: 5' GTGGTGGTCCATGTTCCTG 3'
- homo sapiens, COX-2 (NM_000963.2) Fw: 5' TGGGAAGCCTTCTCTAACCTC 3'
  Rev: 5' TCAGGAAGCTGCTTTTTACCTT 3'
- homo sapiens, LPGDS (NM_000954.5) Fw: 5' AGAAGAAGGCGGCGTTGTCC 3'
  Rev: 5' CCACCACTGACACGGAGTAGG 3'
- homo sapiens, HPGDS (NM_014485.2) Fw:5'GAGAATGGCTTATTGGTAACTCT GT 3'
  Rev: 5' AAAGACCAAAAGTGTGGTACTGC 3'
- homo sapiens, mPGES1 (NM_004878.4) Fw: 5' CGCTGCTGGTCATCAAGA 3'
  Rev: 5' CGTGTCTCAGGGCATCCT 3'

Expression of the gene of interest was normalized to the expression of the ribosomal protein S6 gene (S6), which was measured in parallel as an internal control. All experiments were analyzed using stepOnePlus software.

If the difference in C_t values of duplicates was larger than two, and the mean was larger than the lowest C_t value of the white duplicates, patients were excluded from the analysis for the gene.

Ex vivo muscle motility studies

Seven tissue samples from patients not included in the ERP or NERP groups were collected and used immediately to perform a motility assessment. These patients underwent colorectal resection and followed an enhanced recovery program. After their surgical resection, the samples were immediately placed in cold HBSS for transfer to the laboratory. Strips of circular and longitudinal muscle were dissected and placed in an organ bath (Radnoti, California, USA) with 15 mL of Krebs solution at 37°C, continuously bubbled with 95% O_2 and 5% CO_2. The contractile responses of the muscle strips were continuously recorded using isometric force transducers (No. TRI202PAD, Panlab, Cornellã, Spain) coupled to a computer equipped with the PowerLab 8/30 system and LabChart data analysis software (AD Instruments, Spechbach, Germany). The strips were stretched with a preload of 1g, which was maintained during an equilibration period of 60 minutes. Thereafter, they were subjected to electrical field stimulation (EFS) using a STG 4008 MCS electrical stimulator (Multi Channel Systems, Reutlingen, Germany). EFS parameters were: train duration, 10 seconds; pulse frequency, 20Hz; pulse duration, 400µs; pulse amplitude, 11V. This procedure was repeated three times at 10-minute intervals. Then, 15 µl of the drugs listed hereafter were added to the baths and after 30 minutes of incubation, the same EFS stimulation protocol was repeated.

Drugs were (i) a mPGES1 inhibitor (CAY10589) used at a final concentration of 10 µM (Cayman Chemical, Ann Arbor, USA) and (ii) prostaglandin D synthase (hematopoietic-type) inhibitor I (H-PGDS Inhibitor I) used at a final concentration of 1 µM (Cayman

Chemical). Both were solubilized in DMSO at a concentration of 10 mM and 1 mM respectively. Concentrations were determinated according to the furnisher recommendations. Contractile activity was evaluated by measuring the area under the curve (AUC). Spontaneous contractile activity was evaluated by measuring the AUC for two minutes before the first EFS. The EFS-induced response was evaluated by measuring the AUC during the EFS period and one minute after stimulation.

The amplitudes of spontaneous and induced contractions were also measured during the same period.

Statistical analyses

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL) and Prism software. Data were expressed as median (interquartile range). The Mann Whitney U was performed to compare non-normal continuous variables. Linear regressions were done for variables likely to have an association with delay to recovery. $p<0.05$ was considered as significant.

Results

ERP vs NERP patients

Overall, 39 patients were included. Twenty-eight were men (71.8%) and the median body mass index was 27 kg/m^2. On baseline, patients were comparable (*supplementary file 1*) apart for diabetes occurrence, which was more frequent in the NERP group (p=0.040) and ASA-score that was higher in NERP group (p=0.03). The rate of surgical laparoscopic access was higher in the ERP group (p<0.005) but this difference was expected because surgical access was an item of the ERP.

Arachidonic acid metabolism and enhanced recovery programs

We first characterized the impact of ERP on the presence of mucosal *mRNA* for enzymes involved in AA metabolism. There was no significant modification of mucosal *mRNA* expression for COX-1 and LPGDS observed in the ERP group in comparison to the NERP group. Interestingly however, COX-2, mPGES1 and HPGDS *mRNA* expressions were significantly reduced by respectively 19-fold (p=0.015), 12-fold (p<0.001) and 8-fold (p=0.004) in ERP patients compared to NERP patients (Figure 1).

Impact of items of enhanced recovery programs on arachidonic metabolism

Given that laparoscopic access reduces postoperative inflammation (33), we aimed to determine whether the difference of *mRNA* expression between groups was exclusively due to this item. Interestingly, comparing patients undergoing laparoscopy (L) and those undergoing laparotomy (NL), HPGDS *mRNA* expression was higher in group NL (p=0.006) but COX-2 and mPGES1 *mRNA* expression was not significantly different between groups (respectively p=0.648 and p=0.060) (Figure 2).

Furthermore, in linear regression, we found that HPGDS and mPGES1 *mRNA* expression was associated with the number of items of ERP compliance (respectively r2=0.60, p<0.0001 and r2=0.25, p=0.002) (Figure 3) but COX-2 was not (r2=0.01, p=0.588).

Acid arachidonic metabolism and postoperative ileus in patients following an enhanced recovery program

We then aimed to determine whether, within the ERP patient population, *mRNA* expression for enzymes involved in AA metabolism was associated with POI (POI-patients) and postoperative GI motility recovery.

First, we determined that mucosal *mRNA* expression of the present genes of interest was similar between POI and non-POI (NPOI) patients (Table 2 and Figure 4 A, B and C). Second, we characterized the expression of these genes in the muscularis propria and found no change in COX-2 (p=0.08), mPGES1 (p=0.90) or HPGDS (p=0.85) *mRNA* expression between POI and NPOI patients (Figure 5 A, B and C).

Third, we determined whether *mRNA* expression for enzymes involved in AA metabolism correlated with GI function recovery elements, i.e. delay to first flatus, first stool and GI motility recovery (table 2). Mucosal HPGDS *mRNA* expression was not significantly associated with delay to first flatus (r2=0.13; p=0.07). In mucosal specimens, no difference of mRNA expression was found for all genes (Figure 4 D, E and F; Table 2). In the muscularis propria, COX-2 *mRNA* relative expression was significantly correlated with delay to first flatus (p=0.04). Furthermore, HPGDS *mRNA* relative expression was significantly correlated between delay to GI motility recovery (p=0.002) and first stool (p<0.008) (Table 2 and Figure 5F; r2=0.22; p=0.002). However, mPGES1, COX-2 and LPGDS *mRNA* expressions were not significantly correlated with GI function recovery (Table 2; Figure 5D and E).

Impact of HPGDS inhibitor I and mPGES1 inhibitor on ex vivo colon motility

In the final step, to determine whether AAM located downstream of COX-2 and associated with recovery of GI motility *in vivo* could affect GI motility *ex vivo*, we characterized the effects of specific HPGDS (H-PGDS inhibitor I) and mPGES1 (CAY10589) inhibitors on the *ex vivo* contractile activity of colonic circular muscle strips.

DMSO, at the drug equivalent final concentration used to dissolve the antagonist (1:1000), had no effect on spontaneous muscle activity (Figure 6A). Surprisingly, H-PGDS inhibitor I had no effect on spontaneous colonic motor activity (Figure 6B).

CAY10589 led to a significant increase in contractile activity ($p=0.03$; $n=7$) (Figure 6C and 6D). Finally, there was no significant increase of the amplitude of the peak contraction ($p=0.11$; $n=7$) (Figure 6E).

Discussion

In the present study, we first showed that patients who underwent colorectal tumor resection and followed an ERP had an early reduced colonic mucosal COX-2, mPGES1 and HPGDS *mRNA* expression, when compared to colorectal resection patients who did not follow an ERP. Laparoscopic access has been thought to be the cause of this difference because it is known to reduce postoperative inflammation [33], and it was also used significantly more in the ERP group. However, we showed that it was not the only parameter involved in the reduction of *mRNA* expressions. Indeed, only the HPGDS *mRNA* expression differed between group L and NL (p=0.006). Also, we showed that expressions of mPGES1 and HPGDS *mRNA* were significantly reduced when the compliance with ERP increased (respectively p=0.002 and p<0.001), while the COX-2 *mRNA* expression was not. Nevertheless, we cannot explain the reason why COX-2 was not influenced by the number of items followed. We think that this is most likely due to a smaller effect of ERP in reducing COX-2 *mRNA,* requiring a larger number of patients to have significant results. However, this is the first study that shows the role of EPRs in reducing inflammation involving AA metabolism.

This difference can be partly due to laparoscopy but also partly due to immuno-nutrition and carbohydrates loading. Indeed, immuno-nutrition is composed with a part of Arginine. Arginine is involved in nitrogen (NO) metabolism. NO is involved in COX-2 activation [34]. It was shown that, in the early postoperative period, endogenous NO is a major inhibitory component of gastrointestinal motility in rats [35]. Carbohydrates intake, via an increase in blood insulin levels, may also be involved in this reduction of expression, due to the anti-inflammatory effects of insulin, as previously described [36]. Also, the other items of ERP are probably involved in inflammation reduction, but there is little evidence in the literature to explain the pathways and mechanisms of this reduction. However, our results argue for the

fact that not only laparoscopy, but a high compliance of pre- and perioperative ERP reduces early induction of inflammation after colorectal surgery. A linear association between compliance to ERP and gastrointestinal motility recovery has been previously described [15] and can probably be linked to this linear association between compliance and *mRNA* expression.

To further understand POI pathways among ERP patients, we compared mRNA expression of key enzymes involved in AA metabolism between POI and NPOI patients. There was no significant difference, neither in the *mucosa* nor in *muscularis propria*. However, HPGDS *mRNA* expression was positively and linearly correlated with GI motility recovery (p=0.002), whereas COX-2 *mRNA* expression was only correlated with delay to first flatus (p=0.04). This probably means that COX-2 and HPGDS have a residual role in POI despite ERP compliance. To assess their role in muscle contractile activity, we assessed the effect of *ex-vivo* pharmacological inhibition of mPGES1 and HPGDS. mPGES1 inhibition increased spontaneous colon circular muscle contractile activity *ex vivo* in an organ bath (p=0.03), whereas HPGDS did not. We did not assess the effect of COX-2 inhibition because other authors have shown its beneficial effects on muscle contractile activity [22] and because clinical use of COX-2 inhibitors is controversial due to their putative side effects, particularly a potential increase in the risk of anastomotic leakage [37-39]. The adverse effects of non-steroidal anti-inflammatory drugs may be due in part to a blockade of upstream AA pathways, leading to a reduction of various prostanoids exhibiting both deleterious and beneficial effects, such as PGE2 and PGD2 synthesis. Therefore, new selective agents targeting pathways more specifically involved in POI would be of great interest. Similarly to COX-2, our results suggest that ERP reduces the expression of mPGES1, but that mPGES1 still has a role in gastrointestinal motility reduction that could be improved by mPGES1 inhibitors.

From bench to bedside, we argue that mPGES1 could be a good novel therapy to prevent and/or treat POI after colorectal surgery for tumor.

However, our work contains some limitations due to its design and the ethical consideration of patient management. The main limitation was the use of two different cohorts, one prospective and the other retrospective. This choice was made because ERP improved postoperative course of our patients and it seemed difficult to us to propose another management. This resulted in a lack of mucosa in group NERP, leading in the inability to compare mRNA expressions between group in such tissue. However, manipulation essentially increases inflammation in muscularis propria, that is why there is probably incidence on our results.

Also, the 2 groups came from 2 different centers. This probably has no incidence on results because we compared the 2 different managements through these 2 populations.

Some notable differences between our two populations, such as a higher rate of diabetes in the NERP group or a higher ASA-Score in group NERP, were present. Although hyperglycemia has been shown to induce COX-2 synthesis [40], we do not think that the difference in diabetes rates had an influence on GI recovery, given that all patients were treated for the disease at the time of the study, which meant that hyperglycemia was absent. Regarding the ASA score, it could impact on the level of inflammation in the wall of colon and could lead to an increase of significance of difference between groups ERP and NERP but is probably not the only cause of this difference. Indeed, the population of ASA-score > 3 represents only 2 on 11 patients (<20%) and moreover, we showed a significant correlation between inflammation markers and the observance of ERP leading to conclude that ERP reduces the inflammation in colon wall.

One other difference that has to be discussed is the conditions of storage that were different between ERP and NERP groups. However, the delay between collection and freezing was the

same. The only difference was the method of storage in the long-term. All the tissues were firstly frozen in liquid azote and the duration of ischemia that could lead to an increase of inflammation was the same between groups.

Finally, although the cohort of patients is small, the results are significant enough to argue that ERP should be fully complied with in order to have a selective anti-inflammatory effect after colorectal surgery and improve gastrointestinal motility recovery.

Conclusion

Our results suggest that pre- and perioperative phases of ERP prevent the activation of key enzymes of AA pathways, such as COX-2, LPGDS and mPGES-1, and thereby reduce POI. Laparoscopic access is not the only parameter involved in the reduction of POI incidence, and a better compliance would reduce postoperative inflammation.

Furthermore, the effect of ERP on inflammation (and on POI) may be improved using pharmacological inhibition of mPGES-1, but effects of the inhibition of this pathway have to be explored in animal models and further randomized clinical trials.

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Aurélien Venara has been invited to clinical congresses by Nestlé.

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Tables

Table 1: Differences of management between ERP program and traditional program performed before the surgical specimen collection

Table 2: p-values of Mann-Whitney tests and linear regressions according to the gene assessed and the GI function recovered (days) (Significant results in bold)

IR: interquartile range; POI: postoperative ileus; NPOI: no postoperative ileus

Figures

Figure 1: Comparison of the medians of *mRNA* relative expressions of genes for ERP and NERP groups. *$p<0.05$*

Figure 2: Comparison of the medians of *mRNA* relative expressions of COX-2, mPGES1 and HPGDS in mucosa, according to the use of laparoscopic access or not (A, B, C). *$p<0.05$*

Figure 3: Linear regressions of *mRNA* relative expressions of COX-2, mPGES1 and HPGDS according to the compliance of enhanced recovery programs (ERP) (A,B,C)

Figure 4: Comparison of the medians of *mRNA* relative expressions of COX-2, mPGES1 and HPGDS in mucosa, according to the occurrence (POI) or non-occurrence (NPOI) of postoperative ileus (A, B, C), and linear regressions of *mRNA* relative expressions of COX-2, mPGES1 and HPGDS according to delay to recovery of gastrointestinal functions (D, E, F)

Figure 5: In ERP patients, comparison of the medians of *mRNA* relative expressions of COX-2, mPGES1 and HPGDS in muscularis propria, according to the occurrence (POI) or non-occurrence (NPOI) of postoperative ileus (A, B, C), and linear regressions of *mRNA* relative expressions of COX-2, mPGES1 and HPGDS according to delay to recovery of gastrointestinal functions (D, E, F)

Figure 6: *Ex vivo* motility study showing spontaneous contraction with DMSO (A), an inhibitor of mPGES1 (CAY10589; C) and HPGDS inhibitor 1 (B). Dotted line represents the time at which drugs were administered. Administration of CAY10589 results in an increase of spontaneous muscle contraction.

D represents the AUC before and after administration of mPGES1 (p=0.03) and E the maximal amplitude of muscle contraction before and after administration of mPGES1 (p=0.11).

Supplementary files

Table 1: Characteristics and peri- and post-operative course of patients included in the comparative study

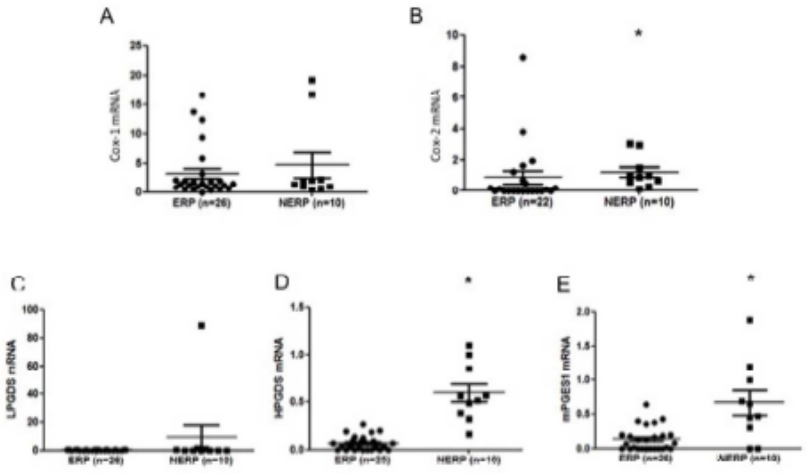
	ERP program	Traditional program
Preoperative		
Patient information	+	-
Immunonutrition (7 days)	+	-
Carbohydrate loading	+	-
Fasting < 6 hours (solids) < 2 hours (liquids)	+	-
Oral bowel preparation	-	-
Peroperative		
Laparoscopic access	+/-	+/-
Reduction of intravenous liquid intake	+	-
Nausea/vomiting prevention	+	-

Table 1: Differences of management between ERP program and traditional program performed before the surgical specimen collection

	COX1			COX2			LPGDS			HPGDS			mPGES1		
	NPOI	**POI**	**p**	**NPOI**	**POI**	**p**	**NPOI**	**POI**	**p**	**NPOI**	**POI**	**p**	**NPOI**	**POI**	**p**
mRNA expression in mucosa															
POI vs NPOI, Median (IR)	1.3 (0.7;2.9)	1.4 (0.9;3)	0.81	0 (0;1)	0.16 (0;0.9)	0.60	0.02 (0;0.09)	0.06 (0.02;0.15)	0.30	0.09 (0.05;0.18)	0.11 (0.04;0.17)	0.77	0.02 (0;0.19)	0.1 (0;0.24)	0.70
mRNA expression in muscularis propria															
POI vs NPOI, Median (IR)	0.72 (0.32;1.5)	1.01 (0.19;1.65)	0.83	0.45 (0.29;1.16)	1.37 (0.57;3.7)	0.08	1.26 (0.43;14,23)	1.89 (0.91;14.87)	0.56	1.32 (0.57;2.15)	0.85 (0.01;5.42)	0.85	2.41 (1.72;2.84)	2.22 (1.03;13.63)	0.90
mRNA expression in mucosa		**r2**			**r2**			**r2**			**r2**			**r2**	
first flatus (linear regression), p		0.01	0.56		0.02	0.49		0.05	0.27		0.13	0.07		0.05	0.28
first stool (linear regression), p		0.06	0.24		0.12	0.11		0.03	0.37		<0.01	0.98		<0.01	0.78
GI motility recovery (linear regression), p		0.05	0.25		0.05	0.29		0.02	0.47		0.02	0.52		<0.01	0.83
mRNA expression in muscularis propria		**r2**			**r2**			**r2**			**r2**			**r2**	
first flatus (linear regression), p		0.12	0.07		0.17	**0.04**		0.03	0.36		0.03	0.37		0.03	0.40
first stool (linear regression), p		0.02	0.42		0.09	0.13		0.03	0.38		0.24	**0.008**		0.02	0.52
GI motility recovery (linear regression), p		0.03	0.35		0.07	0.19		0.03	0.34		0.22	**0.002**		0.10	0.11

	Enhanced recovery program (n=28)	Non-enhanced recovery program (n=11)	Overall (n=39)	p
Gender male, n(%)	20 (71.4%)	8 (72.7%)	28 (71.8%)	0.93
Median age, years	72 (66;80)	78 (68;81)	72 (66;80)	0.40
Body mass index, median, kg/m2	27 (25;29)	29 (28;38)	27 (26;30)	0.10
ASA score, n (%)				**0.03**
2	17 (60.7%)	3 (30%)	20 (52.6%)	
3	11 (39.3%)	5 (50%)	16 (42.1%)	
4	0	2 (20%)	2 (5.3%)	
Missing information	0	1	1	
Medical history, n(%)				
Diabetes	4 (14.3%)	5 (45.4%)	9 (23.1%)	**0.04**
Laparotomy	1 (3.6%)	2 (18.2%)	3 (7.7%)	0.14
Laparoscopy	1 (3.6%)	3 (27.3%)	4 (10.82%)	0.05
Tumor location, n(%)				0.06
Right colon	20 (71.4%)	7 (63.6%)	27 (69.2%)	
Left colon	8 (28.6%)	2 (18.2%)	10 (25.6%)	
Rectum	0	2 (18.2%)	2 (5.1%)	
Dukes classification, (%)				0.13
-	4 (14.3%)	0	4 (10.2%)	
A	5 (17.9%)	0	5 (12.8%)	
B	8 (28.6%)	6 (54.5%)	14 (35.9%)	
C	6 (21.4%)	3 (27.3%)	9 (23.1%)	
D	4 (14.3%)	0	4 (10.3%)	

Missing information	1 (3.5%)	2 (18.2%)	3 (7.7%)	
Laparotomy, (%)	3 (10.7%)	8 (72.7%)	11 (28.2%)	**<0.005**
ERP compliance (median of percentage)				
Pre-operative	100 (80;100)	20 (20;20)	70 (20;100)	**<0.005**
Peri-operative	71 (57;85)	29 (29;29)	57 (28;85)	**<0.005**
Post-operative	78 (71;85)	0	71 (0;85)	**<0.005**
Overall	78 (68;84)	16 (16;16)	68 (19;84)	**<0.005**
Postoperative course				
Post-operative ileus, n (%)	12 (42.9%)	7 (63.9%)	19 (48.7%)	0.1
Nasogastric tube replacement, n (%)	3 (10.7%)	0	3 (9.4%)	>0.5
Post-operative morbidity, n (%)	3 (10.7%)	2 (18.2%)	5 (12.8%)	0.6
First gas (median, days)	2 (1;2)	2 (2;3)	2 (2;2)	**0.04**
First stool (median, days)	3 (2;4)	5 (4;6)	4 (3;4)	**0.01**
GI motility recovery (median, days)	3 (3;4)	5 (4;6)	4 (3;5)	**0.04**
Hospital length of stay (median, days)	7 (5;8)	10 (9;12)	8 (6;12)	**0.02**



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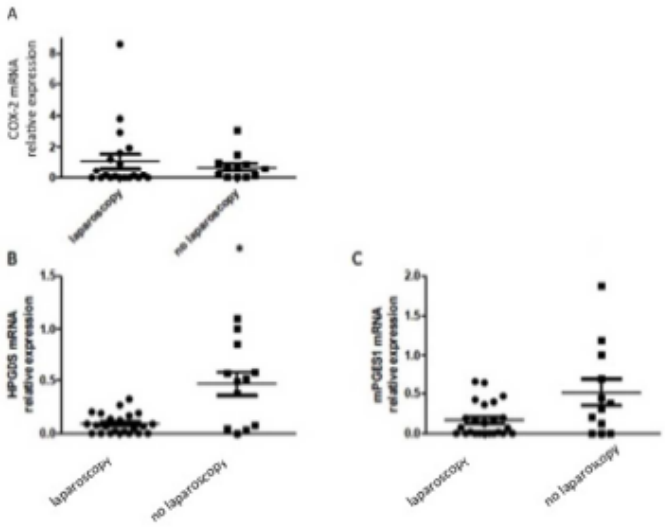

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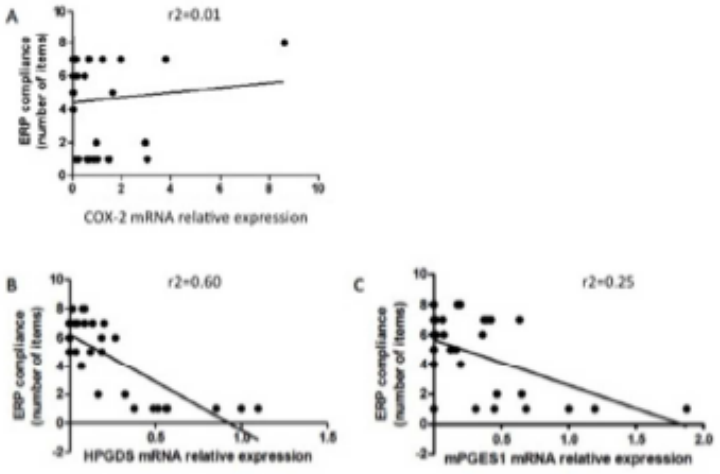

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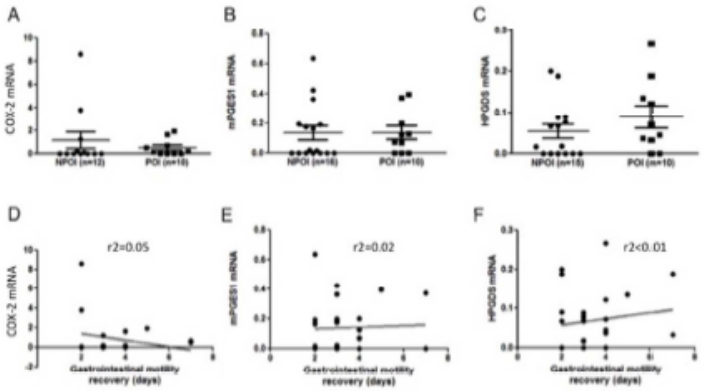

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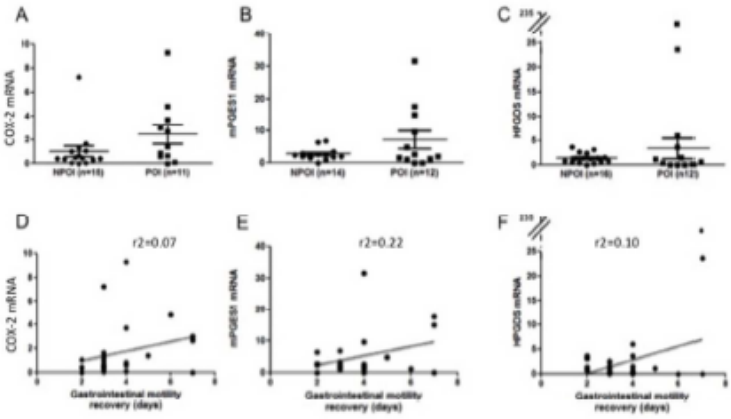

figure 5

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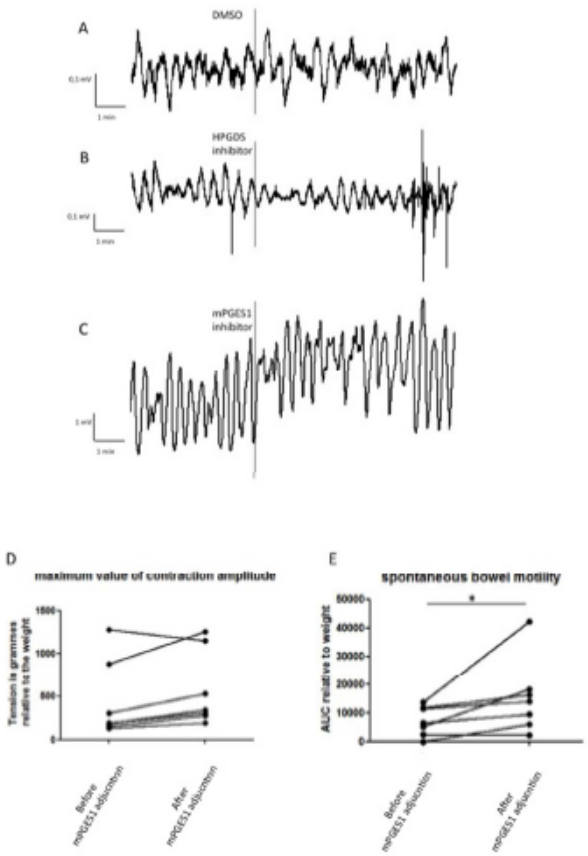

figure 6

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Les résultats de **l'article 5** nous permettent de conclure que la RA entraine une diminution de la synthèse de COX-2, mPGES1 et HPGDS mais que mPGES1 pourrait être une cible de choix pour réduire l'incidence de l'IPO. Afin de limiter l'inflammation, certains auteurs ont étudié des techniques de stimulation vagale par le biais de la mastication de chewing-gum ou d'une stimulation électrique (147,158). Cependant, les terminaisons nerveuses vagues diminuant progressivement sur un sens rostro-caudal, le côlon et le rectum sont peu sensibles à ce genre de stimulation. Deux publications du laboratoire ont mis en évidence une diminution de l'inflammation et une amélioration de la cicatrisation du tissu colorectal par le biais de la neuromodulation sacrée (159,160). La neuromodulation sacrée étant invasive, nous avons choisi de stimuler les terminaisons nerveuses distales, à savoir tibiales postérieures de manière transcutanée. Elle est utilisée dans l'incontinence avec des bons résultats mais aussi dans la constipation avec des résultats moins significatifs (161–163). Nous avons donc proposé d'appliquer cette stimulation dans le contexte de la chirurgie colorectale dans le but de réduire la production de médiateurs lipidiques de l'inflammation et donc l'iléus postopératoire.

F. Article 6 en cours d'écriture pour le British Journal of Surgery

Background : L'IPO implique des mécanismes inflammatoires dans le côlon qui pourraient être prévenus par la neuromodulation sacrée. La TENS peut être utilisé pour mimer la neuromodulation. Le but de cette étude était (i) d'évaluer l'efficacité de la TENS pour réduire le délai de récupération des fonctions GI et (ii) d'évaluer l'efficacité de la TENS de réduire l'apparition des IPO.

Méthode: Quarante patients ayant une chirurgie colique ou rectale de résection étaient inclus dans cette étude et randomisés dans le groupe TENS(T) or placebo(P) selon le site de colectomie et l'abord chirurgical. Le critère de jugement principal était le délai avant la récupération des fonctions GI (reprise des selles et tolérance à l'alimentation solide).

Résultats: Parmi les patients inclus, 34 ont pu être analysés. Deux patients du groupe P ont eu le mauvais appareil remis. En analyse en intention de traiter, le délai moyen de récupération des fonctions GI était de 3,6 et 3,11 jours (respectivement dans le groupe P et T; p=0.60). L'apparition d'un IPO avait plus souvent lieu dans le groupe P (35,3 vs 17,6%; p=0.42) de manière non significative. Le délai d'apparition du premier gaz était plus élevé dans le groupe P (2,24 jours) que dans le groupe T (1,45 jours) (p=0.06). En analyse per protocole, nous avons observé la même tendance, en dehors de l'apparition d'un IPO qui était significativement plus élevé dans le groupe P (p=0.045).

La tolérance pour la TENS était bonne et aucun patient n'a arrêté le protocole.

Conclusion**:** L'utilisation périopératoire de la TENS était sûre et avait des effets prometteurs sur la reprise des fonctions GI. Les résultats de cette étude serviront à faire le calcul d'effectif pour une plus grosse étude prospective multicentrique.

To be submitted to British Journal of Surgery

Perioperative Transcutaneous Tibial Nerve Stimulation would prevent postoperative ileus : a preliminary simple-blind randomized study

Short title: tibial nerve stimulation and postoperative ileus

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Category : Randomized clinical trial registered under the number

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Abstract :

Background: Postoperative ileus(POI)involves inflammatory pathways in colon that could be prevented by sacral nerve modulation. Posterior tibial nerve can be stimulated electrically to mimick neuromodulation. The aims of this study were (i)to assess the efficacy of transcutaneous posterior tibial nerve stimulation(TENS) to reduce the delay gastrointestinal(GI) function recovery and(ii) to assess safety of TENS during perioperative era,(iii) to assess the efficacy of TENS to reduce the occurrence of POI.

Method: Fourty patients undergoing colonic resection were included prospectively in this study and randomized in group TENS(T) or placebo(P) according to the side of colectomy and the surgical access. Primary outcome was the delay for GI functions recovery(stools and solid food tolerance).

Results: Among the 40 patients included, 34 were included in the final analysis. Two patients of group P had the wrong device allocated. In intention-to-treat analysis, mean of delay for GI function recovery was 3.6 and 3.11 days(respectively in group P and T; p=0.60). Occurrence of POI was not significantly higher in group P(35.3 vs 17.6%; p=0.42). Delay for first flatus exoneration was higher in group P(2.24 days) than in group T(1.45 days)(p=0.06). In per protocol analysis, we observed the same trends except occurrence of POI that was significantly higher in group p(p=0.045). Tolerance for TENS was good and no patients did not completed the protocole.

Conclusion: TENS in perioperative era was safe and showed promising effect on GI functions recovery. Results of this study will be usable for sample size calculation in a bigger prospective randomized study.

Keywords : postoperative ileus, prevention, posterior tibial nerve stimulation,

Introduction:

Postoperative ileus (POI) remains a challenge for the surgeon because of its frequency and of the potential severity of its consequences. Enhanced recovery programs (ERPs) reduce the occurrence of POI and the delay to gastrointestinal (GI) functions recovery but POI still occurs in up to 24.4% and mean of GI functions recovers up to 4 days (1,2).

POI is responsible for an increase of the cost of management because it increases the length of stay, but also because it can leads to severe morbidity such as inhalation pneumopathy or cardiac arythmia, can potentially be severe for the patient (3,4). More recently, the link between the physiopathology of POI and anastomotic leakage has been highlighted (5). There is therefore a real need for an improvement of POI prevention or treatment.

In order to improve ERPs, recent clinical trials assessed the efficiency of new therapy such as vagal stimulation by chewing (6,7) or nutritional improvement (8,9) but results are not as relevant as expected. Research always goes on and *Boecxstans et al.* (10) proposed recently electric abdominal vagus nerve stimulation with a significant anti-inflammatory effect leading to expect a significant improvement of GI functions recovery. All these therapies, leading to vagal stimulation, have an effect on small bowel but the effect on colon is more uncertain because it has not been assessed but above all, because vagal nerves density decreases along a rostro-caudal gradient (11). Therefore, a mean for inflammation decrease on colon would be of interest.

We recently showed that, while ERPs decreases the enzymes that synthetized lipidic mediators of inflammation such as COX2 or HPGDS, mPGES1 and that mPGES1 would be a promising target to prevent or to treat POI (12). To do so,

pharmacological or nutritional approaches have to be developed and are not yet usable in clinical practice. However, an instrumental approach reducing colon inflammation in other indication such as ulcerative proctitis has been reported in a case report (13). Indeed sacral nerve stimulation allowed a significant reduction of inflammation in a case of refractive proctitis (13).

Because it is invasive and requires at least two surgical procedure to be implanted, sacral nerve stimulation can not be used to prevent POI but other devices used in urinary and faecal incontinence or constipation stimulate the nerves ending of this nerve (14,15) such as posterior tibial nerve. One of these devices, Urostim 2® (*Schwa-Medico, Ehringshausen, Germany*), is used on a transcutaneous approach and stimulates the tibial nerve transcutaneously. The effect and the safety of use of transcutaneous tibial nerve stimulation (TENS) have been established in the indication of incontinence or constipation but remains to be determined in the context of postoperative course (14,16).

We made the hypothesis that perioperative sacral nerve stimulation by the mean of its terminal roots (e.g tibial nerve) could improve postoperative course in term of delay of GI function recovery.

The first aim was to assess the efficacy of TENS to reduce the delay of GI functions recovery as compared to placebo. The secondary aims were to assess the safety of TENS and its efficacy to reduce the delay for first flatus exoneration or the occurrence of POI, to improve first stools quality, to reduce morbi-mortality after surgery, to reduce the length of stay, to improve the postoperative quality of life of patients and to reduce inflammation parameters in colonic *muscularis propriae*.

Methods:

This was a preliminary randomized single-blind monocentric clinical trial including patients undergoing colon resection, or anterior resection of the high rectum between 01st October 2017 and 02nd May 2017.

The study obtained the Personal Protection Committee approval and was registered on *ClinicalTrials* under the number NCT02815956.

Patients

Criterion of exclusion were : (i) emergency surgery, (ii) Chronic Inflammatory Bowel Disease (CIBD), (iii) documented Irritable bowel disease (IBD), (iv) surgical history of gastrectomy or esogastrectomy (risk of vagal nerve lesion), (v) disease of treatment modifying the metabolism of acetylcholine, (vi) enterostomy, (vii) pace maker because of the risk of interference with the neurostimulator device.

During the period of inclusion, 55 patients underwent colic or high rectal resection and 40 patients were included in this trial (figure 1). The reason for the non-inclusion of the 15 patients were initial problems of organisation for 9 patients (e.g. admission the day of surgery or admission on Sunday or no investigator available), CIBD indication for surgery in 3, location of colectomy on the transverse colon in 2 and subtotal colectomy in 1 (randomisation process allocated did not allow to randomize such colectomies).

Procedure

Randomisation was carried out on-line and stratified according to the location of the colon resected (right *versus* left/high rectum) and according to the surgical access (laparoscopy versus laparotomy).

Patients who accepted the study participation were randomly assigned treatment by Placebo (group P) or by Transcutaneous Tibial Nerve Stimulation (TENS) (group T). Surgical resection of the colon was carried out according to the standard technics. Data collection included:

(i) demographic information : medical history, gender, Body Mass Index (BMI), age.

(ii) data regarding enhanced recovery protocol (ERP) compliance. Enhanced recovery compliance was defined by the percentage of compliance with 18 items observed in the perioperative period. Items collected to assess the compliance with ERP were reported in table 1.

(iii) data regarding surgical procedure(surgical access, duration of procedure, location of colectomy).

(iv) data regarding postoperative course (morbidity classified according to the DIndo-Clavien classification(17), POI occurrence (definition above), need for nasogastric tube reinsertion, length of stay.

(v) Gastro-Intestinal Quality of Life Assessment (GIQLI) (18), quality of first stool assessed by the Bristol stool scale (19).

Endpoints

The primary endpoint was the delay to GastroIntestinal (GI) functions recovery. GI functions recovery was defined by the recovery of stools and tolerance to solid food, as described by Van Bree *et al.* (20).

The secondary endpoints were

- The occurrence of postoperative ileus (POI) and need for nasogastric tube replacement (NGT).

Postoperative ileus was defined the absence of GI functions recovery after POD4.

- The quality of first stool assessed by the Bristol Stool Scale (19).
- The delay before first flatus
- The length of stay
- The quality of life of patients assessed by the Gastro-Intestinal Quality of Life Assessment (GIQLI) (18)
- The inflammatory parameters such as mRNA relative expression Cyclo-Oxygenase 2 (COX-2), Hematopoietic Prostaglandin-D Synthase (HPGDS), microsomal Prostaglandin-E Synthase 1 (mPGES1), Interleukin 6 (IL-6), inducible NitrOxyd Synthase (iNOS) and Monocyte Chemoattractant Protein 1 (MCP1) were also compared between groups. Modality of tissue collection and storage, ARN extraction and Polymerase Chain Reaction (PCR) performance, and of analysis were described in a previous article (12). For this study, six patients of group P and seven patients of group T had samples of muscularis propria collected and stocked in the Biological Resources Center of Angers (BB-0033-00038) and registered under the number CB-2011-05. All these patients were operated on for cancer

Procedures

TENS group (T): Urostim2® (*Schwa-Medico, Ehringshausen, Germany*) device was used to perform the stimulation. Protocol of stimulation was the same as the one use in faecal incontinence. The first electrode was placed back to the internal malleolus and the other one was placed 10 cm higher, on the internal face of the calf. The program P3 was used.

The amplitude of stimulation was ranged up between 10 and 38 mA, with a 200 µs pulse width at a frequency of 10 Hz. The amplitude of stimulation was set according to the patient's feedback.

Stimulation was done the day before surgery. The day of surgery, stimulation was performed only once, at least 2 hours before surgery or at least 2 hours after surgery. The days after surgery, stimulation was performed three times a day, until the gastrointestinal motility recovery. Duration of TENS was 20 minutes.

Placebo group (P): The protocol was exactly the same than for the group T but the device, that seemed exactly like Urostim2®, did not deliver any electrical impulse.

Sample size calculation

As it is a preliminary study, there was no information in literature related to the potential effect of TENS on POI prevention and no sample size calculation has been performed. Twenty patients group were *a priori* assigned in each group to quantify this effect.

Statistical analysis

Following descriptive analysis, we compared patients from group P with patients from group T.

Data were expressed as number and percentage, and Fisher's or Chi-Square tests were used as appropriate for the comparison of categorical variables.

Data were expressed as mean (+/-standard deviation (SD)) or median (interquartile range (IQ)) and t-test or Mann-Whitney U test were employed as appropriate to compare continuous variables.

$P<0.05$ was considered statistically significant. Data analysis was performed with the Statistical Package for the Social Science version 15 Software (SPSS, Chicago, IL).

Results:

Forty patients were recruited and randomized. Among these patients 6 were excluded because of consent problems or contraindications (Figure 1). Patients excluded did not follow the protocol and were not taken in account in the final analysis. Finally, 34 patients were analysed.

Twenty-one patients were male (61.8%). Surgery was completed in every cases and median of the duration of the procedure was 167 minutes (120;220). Twenty-seven patients had left colectomy (79.4%) and 29 patients had a laparoscopic procedure. Conversion in open was necessary in 9 cases (31%). Compliance with enhanced recovery program was > 70% in 26 patients (76.6%).

POI occurred in 9 patients (26.5%) and 4 patients required NGT replacement (11.8%). With the exception of POI, 1-month morbidity occurred in 11 patients (32.4%) and 1 patient of them had 2 complications. Morbidity collected was: acute urinary retention (n=3), pneumopathy (n=2), postoperative bleeding (n=2), epilepsy (n=1), incisional hernia (n=1), small bowel obstruction occurring after GI functions recovery (n=1), postoperative hyperthermia (n=1), urinary infection (n=1).

Except for the patient experiencing epilepsy (group T) that had a Dindo-Clavien morbidity 4A and the patient experiencing small bowel obstruction (group P) that needed a reintervention and had a DIndo-Clavien morbidity 3A (group T but device P allocated), all the complications were Dindo-Clavien ≤ 2.

No death was reported.

Intention to treat (ITT) analysis (Table 2)

Seventeen patients were assigned in each group. At baseline the 2 groups were well matched.

Mean of GI functions recovery was 3.59 days in group P and 3.12 days in group T but there was no significant difference (p=0.40).

Other secondary outcomes were not significantly different (table 2) but first flatus exoneration occurred later in group P (2.24 days) than in group T (1.47 days) (p=0.06).

NGT was more likely to be replaced in group P (17.6%) than in group T (5.9%) (p=0.6) and POI was more likely to occur in group P (35.3%) than in group T (17.6%) (p=0.44). Morbidity was not significantly different between groups (p=0.27) but rate of complication was more important in group P (41.2%) than in group T (23.5%).

Median of first stool quality assessed by Bristol stool scale was not significantly different between groups (respectively p=0.44).

COX2, mPGES1, MCP1, IL6 and HPGDS mRNA expression *in muscularis propria* were not significantly different between groups (respectively p=0.86, p=0.17, p=0.58, p=0.86, p=0.41). *mRNA* expression of iNOS was measurable only in 2 patients of group P.

Per-protocol (PP) analysis (Table 3)

Due to the wrong allocation of 2 devices, we performed also PP analysis (Figure 1). Finally, 19 patients received the placebo (group P) and 17 patients received the stimulation (group T).

At baseline, the 2 groups were well matched. There was no significant difference between groups regard patients' or surgical characteristics (Table 2).

Mean of GI functions recovery was 3.74 days in group P and 2.87 days in group T but there was no significant difference (p=0.10).

Other secondary outcomes were not significantly different (table 2) but first flatus exoneration occurred later in group P (2.16 days) than in group T (1.47 days) (p=0.07).

POI occurred significantly more in group P (n=8, 42.1%) than in group T (n=1, 6.7%) (p=0.045) and nasogastric tube had to be replaced in 4 patients (11.8%), of group P but none in the group T (p=0.27).

Morbidity was not significantly different between groups (p=0.27) but the rate of complication was more important in group P (42.1%) than in group T (20%).

Median of first stool quality assessed by Bristol stool scale and postoperative quality of life assessed by GIQLI were not significantly different between groups (respectively p=0.44 and p=0.44).

mRNA expression of mPGES1 tended to be higher in group P than in group T (p=0.056) (figure 2A). There was no significant difference of *mRNA* expression of HPGDS and iNOS but there was no measured expression of these enzymes in group T (figure 2B and 2C).

COX2, MCP1 and IL-6 *mRNA* expressions were not significantly different between groups (respectively p=0.93, p=0.63, p=0.88).

Adverse effects potentially linked with TENS and tolerance to TENS

No complication directly linked to TENS was reported but one patient of group TENS experienced epilepsy. As industry recommends caution with epileptic patients when using TENS, we secondarily considered epilepsy as a criterion of exclusion.

No patient stopped the protocol because of bad tolerance to TENS. Also, the GIQLI was not different between the 2 groups (p=XX in ITT and p=0.40 in PP).

Discussion:

This preliminary RCT included 40 patients undergoing colorectal resection but 34 patients completed the protocol and were included in the final analysis.

Difference observed between groups regarding GI function recovery were not significant, nor in ITT analysis, nor in PP analysis. However, while the difference was not significant, we observed a reduction in the delay of recovery from 13% (ITT) to 23.3% (PP). Despite its limitations inherent to the preliminary characteristic of this RCT but also inherent to the bias of procedure (wrong allocation of devices and secondary exclusion), our study completed its first aim that was to quantify the effect of TENS on patients' recovery after colorectal surgery.

Interestingly, and despite the fact that no significant difference between groups was expected regarding our secondary aims, POI occurence was significantly higher in the group P (n=8; 42.1%) than group T (n=1; 6.7%) (p=0.045) in PP analysis. This result was not as significant in ITT analysis than in PP analysis but we noted a trend of POI reduction in group T (35.3 vs 17.6%; p=0.42). Occurrence of POI in our series (26.5%) was similar with the one reported in literature in a population of patients following ERPs (1). However, the rate of POI in the group P that was expected to be as much important as literature was higher. This is probably due to the small number of our population that lead to a bias. However, there was no difference between groups regarding the usual risk factors for POI such as male gender (21–23), history of abdominal surgery (24), open access (p=0.63) and conversion to open (23), right side of colectomy (25), duration of surgery (22) or ERPs compliance (1) confirming than groups were well matched in ITT or PP analysis.

Regarding consequences of POI, NGT was more likely to be replaced in group P than in group T (p=0.60 in ITT analysis and p=0.27 in PP analysis). While this was

not statistically significant, this data is interesting confirming that high grade POI (26) were more likely to occur in group P.

Data regarding delay to first flatus were of interest in PP and in ITT analysis (respectively p=0.07 and p=0.06). Observed reduction of delay was 32% in PP or 34% in ITT. This data will allow sample size calculation for more powerful analysis.

Considering that anastomotic leakage is associated with POI occurrence (OR=12.57) (5), we thought that TENS could impact on postoperative morbidity. Our results support this supposition showing a non significant reduction of morbidity from near 50% in group T as compared to group P (in PP but also in ITT analysis). However, morbidity occurring in our study was low grade morbidity and no fistula was reported.

To add some evidence to advocate for a real beneficial effect of TENS on postoperative course after colorectal resection, *mRNA* expression of some enzyme early involved in inflammation pathway was quantified. While because of the small number of patients and of POI occurrence, results were not statistically significant, a reduction of mPGES1 mRNA expression was observed in PP analysis (p=0.056) as in ITT analysis (p=0.17). This enzyme has been previously found to be a potential target to prevent or treat POI after colorectal surgery (12). Interestingly, other enzymes such as iNOS or HPGDS were also reduced but the level of expression was very low and the risk of bias is important in such small population. However, literature reports these enzymes to be involved in POI physiopathology (12,27) and their reduction is compatible with the beneficial effect of TENS on POI.

Finally, TENS has been successfully used in every patient following the protocol and we did not report any severe adverse effect directly due to the use of TENS. No patient experimented local cutaneous inflammation or pain. Only one

patient experimented a crisis of epilepsy. The patients had a severe history of epilepsy and his treatment was suspended in the perioperative era. However, even if the link between this episode and the TENS is uncertain, we chose to contraindicate TENS in patients with medical history of epilepsy.

Despite some limitations inherent to its preliminary characteristic and to the several deviations from the protocol (secondary exclusions of patients), this preliminary RCT provides some interesting information usable for the calculation of sample size patients for future multicentre RCTs. Indeed, we observed some difference in delay for GI functions recovery, first flatus recovery and in the occurrence of morbidity and POI between groups. This RCT completed its objectives showing these differences, but also confirming that the use of TENS is safe in perioperative course.

Conclusion :

Use of TENS is feasible and safe in perioperative course and TENS seems to have some effect on GI recovery but also on morbidity occurrence. This effect remains to be confirmed and characterized on high recruitment multicentre double-blinded RCTs. Results of this preliminary study will be used for the sample size calculation of these RCTs.

Conflict of interest: Schwa Medico® graciously lent the devices needed for the study.

The authors declare no conflict of interest directly linked to this RCT.

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Figures

Figure 1 : Flow chart of the pre-TAPIOCA's population.

Figure 2 : mRNA expression of the different enzymes of lipidic metabolism (A) mPGES1, (B) HPGDS and (C) iNOS. None were statistically significant.

Tables :

Preoperative era (N=6)	Peroperative era (n=7)	Postoperative era (n=4)
Patient information about the program	Laparoscopic access	POD 0 mobilisation
Preoperative Immunonutrition	Nasogastric tube ablation	Early feeding
Preoperative immunonutrition	No surgical drain	Pulmonary physiotherapy
Colonic prepation	Dexamethasone injection	Venal hydrosodic injection restriction
Carbohydrates (POD -1)	Nausea prevention	
Carbohydrates (POD 0)	Venal hydrosodic injection restriction	
Fasting	Hypothermia prevention	
	Multimodal analgesia	

Table 1 : Enhanced recovery programs items collected.

POD: Postoperative day

	Group P (n=17)	Group T (n=17)	Overall	p
Gender male, n (%)	10 (58 .8%)	11 (64.7%)	21 (61.8%)	0.72
Median of age, years (IQ)	66.6 (61.3;68.1)	67.5 (60.9; 72.1)	67.1 (61 ;71)	
Median of BMI, kg/m2 (IQ)	25.3 (22 ;27)	24.6 (23 ; 26.9)	25.3 (22.4 ;27)	
Medical History, n (%)				
None	2(11.8%)	4(23.5%)	6 (17.6%)	0.66
Diabetes	1 (5.9%)	2 (11.8%)	3 (8.8%)	>0.90
Hypentension	6 (35.3%)	8 (47.1%)	14 (41.2%)	0.48
Coronaropathy	1 (5.9%)	0	1 (2.9%)	>0.90
Other cardiac pathology	7 (41.2%)	5 (29.4%)	12 (35.3%)	0.47
laparotomy	3 (17.6%)	1 (5.9%)	4 (11.8%)	0.60
Median of duration of surgery, min (Q)	152.5 (117 ;226.5)	187.5 (120 ;212.5)	167.5 (120 ;220)	
Surgical Access, n (%)				
Laparotomy	2 (11.8%)	3 (17.6%)	5 (14.7%)	>0.90
Laparoscopy	15 (88.2%)	14 (82.4%)	29 (85.3%)	
if laparoscopy, conversion	5 (33.3%)	4 (28.6%)	9 (31%)	>0.90
Type of colectomy				0.52
right	3 (17.6%)	4 (23.5%)	7 (20.6%)	
left	14 (82.4%)	12 (70.6%)	27 (79.4%)	
Right and left	0	1 (5.9%)	1 (2.9%)	
Compliance with ERPs > 70%, n (%)				
Morbidity (exclusion of POI), n(%)	7 (41.2%)	4 (23.5%)	11 (32.4%)	0.27
Postoperative ileus, n (%)	6 (35.3%)	3 (17.6%)	9 (26.5%)	0.42
Need for NGT replacement, n(%)	3 (17.6%)	1 (5.9%)	4 (11.8%)	0.60
Mean of time to first flatus, days (+/-SD)	2.24 (+/-0.35)	1.47 (+/-0.17)	**1.85 (+/-1.18)**	0.06
Mean of time to GI functions recovery, days (+/-SD)	3.6 (+/-0.44)	3.11 (+/-0.33)	**3.35 (+/-1.59)**	0.40
Median of Bristol Stool Scale, (IQ)	4 (4 ;5)	4 (4 ;4)	4 (4 ;5)	
Median of GIQLI, (IQ)	94.5 (70.5 ;111)	**82 (72;82)**	83.5 (72 ;100)	
Mean of hospital stay, days (+/-SD)	7.71 (+/-0.44)	7.47 (+/-0.33)	**7.59 (+/-3.6)**	0.85

Table 2: Comparison of group P and Group T regarding patients' and surgical characteristics, and early postoperative outcomes in Intention to treat analysis.

Significant variables are in bold.

IQ : Interquartile; ERPs : Enhanced Recovery Protocols; POI : Postoperative Ileus; NGT : Nasogastric tube; GIQLI : Gastro-Intestinal Quality of Life Index

	Group P (n=19)	Group T (n=14)	Overall	p
Gender male, n (%)	12 (63.2%)	9 (60%)	21 (61.8%)	0.85
Median of age, years (IQ)	66 (61.3 ;68.1)	67.5 (62.2 ;71.9)	67.2 (61;70.8)	0.27
Median of BMI, kg/m2 (IQ)	25.3 (22 ;27)	24.62 (23 ;28)	25.3 (22.4;27)	0.58
Medical History, n (%)				
None	4 (21.1%)	3 (20%)	7 (20.6%)	>0.90
Diabetes	1 (5.3%)	2 (13.3%)	3 (8.8%)	0.57
Hypentension	6 (31.6%)	8 (53.8%)	14 (41.2%)	0.20
Coronaropathy	1 (5.3%)	0	1 (2.9%)	>0.90
Other cardiac pathology	8 (42.1%)	4 (26.7%)	12 (35.3%)	0.35
laparotomy	3 (15.8%)	1 (6.7%)	4 (11.8%)	0.61
Surgical Access, n (%)				
Laparotomy	2 (10.5%)	3 (20%)	5 (14.7%)	0.63
Laparoscopy	17 (89.5%)	12 (80%)	29 (85.3%)	
if laparoscopy, conversion	6 (35.3%)	(3 (25%)	9 (31%)	0.69
Type of colectomy				>0.9
right	4 (21.1%)	3 (20%)	7 (20.6%)	
left	15 (78.9%)	12 (80%)	27 (79.4%)	
Right and left	0	1 (5.9%)	1 (2.9%)	
Median of duration of the procedure, min (IQ)	152.5 (120 ;219)	187 (120 ;230)	167.5 (120;220)	0.56
Compliance with ERPs > 70%, n (%)	13 (68.4%)	13 (86.7%)	26 (76.5%)	0.26
Morbidity (exclusion of POI), n(%)	8 (42.1%)	3 (20%)	11 (32.4%)	0.27
Postoperative ileus, n (%)	**8 (42.1%)**	**1 (6.7%)**	**9 (26.5%)**	**0.047**
Need for NGT replacement, n(%)	4 (21.1%)	0	4 (11.8%)	0.11
Mean of time to first flatus, days (+/-SD)	2.16 (+/-0.32)	1.47 (+/-0.19)	1.85 (+/-1.18)	0.07
Mean of time to GI functions recovery, days (+/-SD)	3.74 (+/-0.32)	2.87 (+/-0.40)	3.35 (+/-1.59)	0.10
Median of Bristol Stool Scale, (IQ)	4 (4 ;5)	4 (4 ;4)	4 (4 ;5)	0.44
Median of GIQLI, (IQ)	94.5 (70 ;111)	82.5 (72 ;86)	83.5 (72 ;100)	0.44
Mean of hospital stay, days (+/-SD)		7.4	7.59 (+/-3.6)	

Table 3: Comparison of group P and Group T regarding patients' and surgical characteristics, and early postoperative outcomes in Per-Protocol analysis.

Significant variables are in bold.

IQ : Interquartile; ERPs : Enhanced Recovery Protocols; POI : Postoperative Ileus;

NGT : Nasogastric tube; GIQLI : Gastro-Intestinal Quality of Life Index

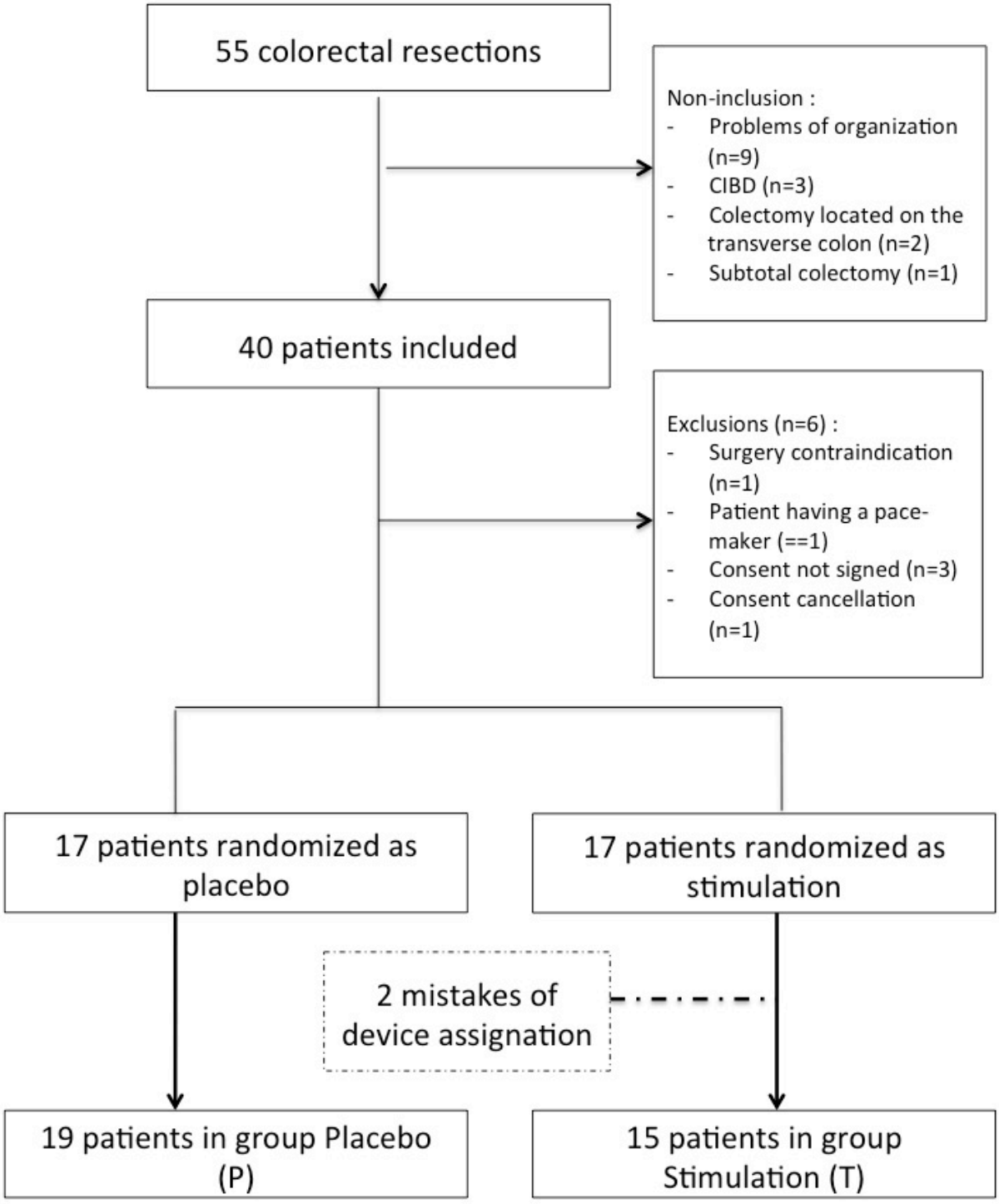

Figure 1 : Flow chart of the pre-TAPIOCA's population.

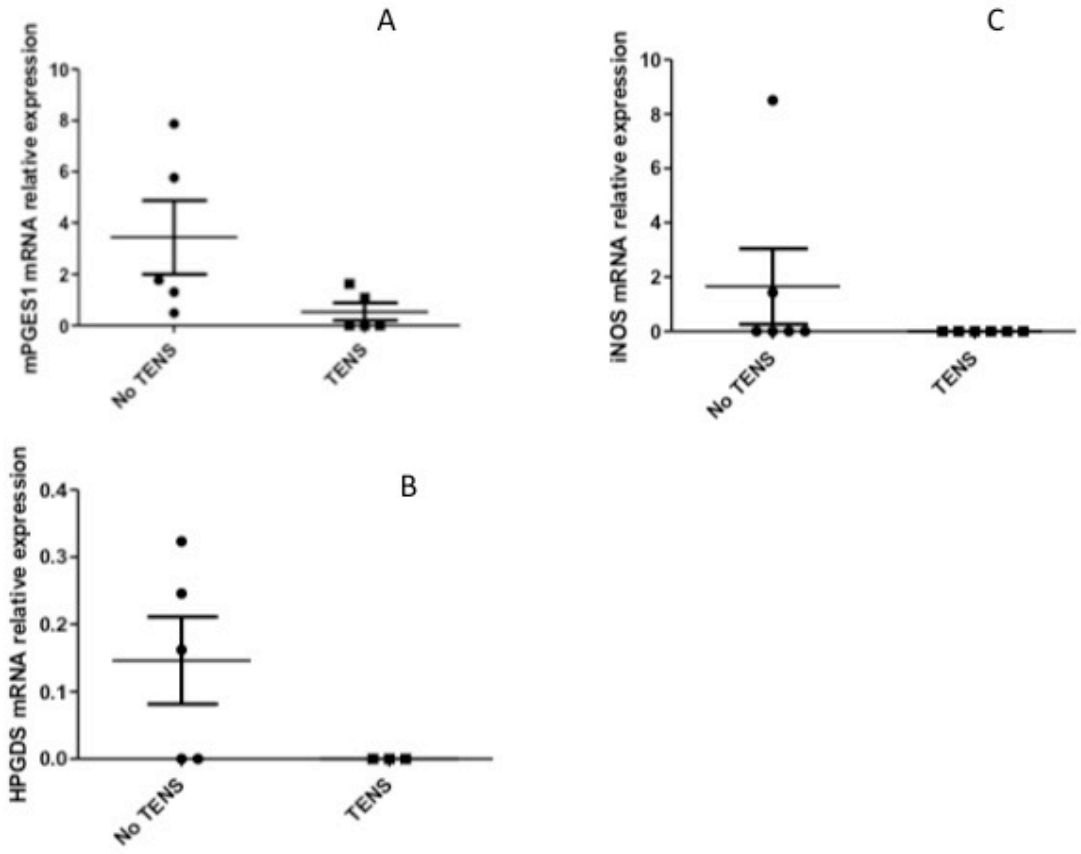

Figure 2 : mRNA expression of the different enzymes of lipidic metabolism (A) mPGES1, (B) HPGDS and (C) iNOS. None were statistically significant.

G. Mise en place d'un modèle murin

Si nous avons pu identifier la TENS comme prometteuse pour réduire la durée de l'iléus, il reste encore à définir l'intérêt in vivo de l'inhibition pharmacologique de la mPGES1 dans ce but. Par ailleurs, il reste aussi à définir d'autres facteurs nutritionnels ou instrumentaux qui pourraient avoir le même effet, sans effet secondaire, notamment sur la cicatrisation anastomotique. Dans ce but, nous avons mis en place un modèle d'iléus murin au sein du laboratoire. Ce modèle a pu être développé sur des souris « standards » mais la disponibilité de souris mPGES1 KO peut être un atout dans la recherche d'autres voies de signalisation. Par ailleurs, ce modèle murin permettra la réalisation d'études précliniques de ciblage thérapeutique.

Ce modèle a été développé à partir de la littérature et notamment des travaux de Boeckxstaens *et al.* ou Bauer *et al.* (65,164). Afin de valider l'efficacité de notre modèle et le retentissement de notre protocole sur le transit gastrointestinal, 4 groupes de souris C57BL6 recevaient une intervention différente. Après avoir été endormie par un mélange anesthésique de Imalgène et Rompun et après avoir reçu une analgésie de type buprécare, un groupe de souris ne recevait pas d'intervention (groupe « anesthésie »), un groupe recevait une simple laparotomie d'environ 1 cm de longueur (groupe laparotomie) et un groupe recevait une laparotomie et se voyait manipulé l'intestin à l'aide d'un coton tige (après éviscération, à l'exclusion du duodenum et du côlon (figure 8)) (groupe manipulation intestinale). Un autre groupe ne recevait aucune intervention (groupe témoin).

Figure 8 : Modèle Murin d'iléus avec manipulation intestinale. Eviscération par un orifice d'environ 1 cm de long.

La laparotomie médiane est fermée par des points séparés de vicryl 4.0.

Trois heures après le réveil les souris sont gavées par 120 microL de rouge carmin et de carboxyméthylcellulose dilués dans l'eau distillée. Le sacrifice des souris, dont les souris témoins, a lieu 1h30 après le gavage. Le transit du rouge carmin est mesuré et nous avons pu constater qu'il diminue de manière significative en fonction de l'importance de notre intervention sur le tube digestif (figure 9), ce qui nous a permis de confirmer notre modèle d'étude.

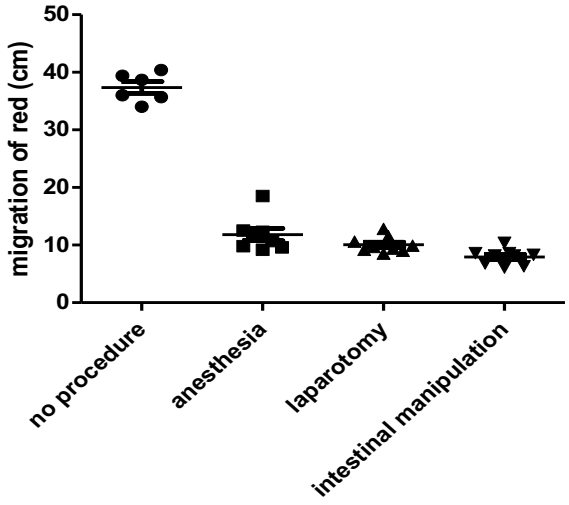

Figure 9 : Front de migration du rouge carmin après 1h30

IX. Annexes

A. Annexe1 : Mise au point parue dans le Journal of Visceral Surgery

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REVIEW

Postoperative ileus: Pathophysiology, incidence, and prevention

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Summary Postoperative ileus (POI) is a major focus of concern for surgeons because it increases duration of hospitalization, cost of care, and postoperative morbidity. The definition of POI is relatively consensual albeit with a variable definition of interval to resolution ranging from 2 to 7 days for different authors. This variation, however, leads to non-reproducibility of studies and difficulties in interpreting the results. Certain risk factors for POI, such as male gender, advanced age and major blood loss, have been repeatedly described in the literature. Understanding of the pathophysiology of POI has helped combat and prevent its occurrence. But despite preventive and therapeutic efforts arising from such knowledge, 10 to 30% of patients still develop POI after abdominal surgery. In France, pharmacological prevention is limited by the unavailability of effective drugs. Perioperative nutrition is very important, as well as limitation of preoperative fasting to 6 hours for solid food and 2 hours for liquids, and virtually no fasting in the postoperative period. Coffee and chewing gum also play a preventive role for POI. The advent of laparoscopy has led to a significant improvement in the recovery of gastrointestinal function. Enhanced recovery programs, grouping together all measures for prevention or cure of POI by addressing the mechanisms of POI, has reduced the duration of hospitalization, morbidity and interval to resumption of transit.

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Key points
- There is no consensual definition of a normal interval to resumption of transit resulting in non-reproducible results in studies of postoperative ileus.
- Postoperative ileus occurs following 10 to 30% of abdominal surgeries.
- The main risk factors are male gender, advanced age and the volume of blood loss.
- Ileus occurs in three phases: a neurological phase, an inflammatory phase, and a phase of activation of the vagal nervous system.
- In France, pharmacological prevention is limited by the non-availability of effective drugs.
- Enhanced recovery after surgery programs make use of several measures aimed at the different phases of ileus to reduce the interval to ROT.

Introduction

Postoperative ileus (POI) has become a public health problem because of its role in postoperative morbidity and increased hospital stay [1—3]. Its reported rate of incidence varies among different authors and specialties, but is generally between 10 and 30% for abdominal surgery [4—11]. The consequences of POI can be severe since it causes gastrointestinal stasis with a risk of nausea and vomiting, which can be complicated by pulmonary aspiration. Besides this extremely serious complication, POI may also cause dehydration, electrolyte imbalance, or sepsis.

Recent recommendations for perioperative management (initially proposed by the ERAS group [12] and thereafter by the GRACE Association [13]) have enabled a net decrease in hospital stay and morbidity, but also a decrease in the interval to resumption of transit (ROT) [14—17]. ERAS management protocols include preoperative measures (patient information, sweetened oral liquids, no bowel preparation, avoidance of routine anxiolytic premedication, reduction of preoperative fasting period to 2 hours for liquids and 6 hours for solids), intraoperative measures (preference for laparoscopic approach, avoidance of bladder, gastric and abdominal drains, optimal fluid replacement based on suitable monitoring, avoidance of long-acting opioids, active measures to combat hypothermia, nausea and vomiting), and postoperative measures (immediate postoperative removal of the nasogastric tube, feeding on the evening of the intervention, a multimodal analgesic program, mobilization on the evening of surgery, removal of the bladder catheter on day 1 [D1], limitation of postoperative intravenous fluids, thromboprophylaxis, digestive stimulation by gum chewing, and carbohydrate loading [18,19]. The purpose of enhanced recovery programs is to reduce perioperative stress, in hope of facilitating the return of patient autonomy.

The mechanisms that reduce the interval to ROT are beginning to be understood, but much more remains to be determined. It is probably for this reason that no author has managed to propose a consensual cut-off interval for defining POI and that treatment and prevention of POI are only partially effective.

This review is intended to update knowledge with regard to POI, and to describe each measure used to combat POI as it derives from our pathophysiological understanding of the condition. Better understanding of POI provides insight into clinical studies in a context where there is no consensual definition.

Definition and risk factors

POI is a physiological arrest of gastrointestinal transit in response to surgical stress. In 2005, Kelhet et al. underscored the need for a consensual definition of POI, especially regarding what constitutes a normal time interval to ROT [20]. In 2016, several authors have noted the persistent lack of such a definition [17,21].

In the literature, various qualifiers have been applied to POI: ''pathological'' or ''prolonged'' (longer than the presumed normal duration), or ''secondary'' (linked to extrinsic causes such as postoperative peritonitis...).

In 2013, Vather et al., in their conclusions to a meta-analysis, proposed a clinical definition of POI [10] defined by the combination of at least two of the following five signs on or after the fourth postoperative day, with no improvement since surgery:
- nausea and vomiting;
- an inability to tolerate solid or semi-liquid diet during the preceding 24 hours;
- no gas or stool for the preceding 24 hours;
- abdominal distension;
- radiological evidence of ileus.

These data were confirmed in the works of van Bree et al. [22] who considered the best endpoint to define ROT to be the combination of passage of stool and tolerance of solid food.

However, there is still no real consensus for a ''normal'' interval that would distinguish between pathological POI and physiological POI. The cut-off limit used by various authors to describe pathological POI varies from 1 to 7 days (Table 1) and this variable limit leads to non-reproducibility of studies dealing with POI because their rates vary from one to threefold for different teams. For example, in the same patient population and depending on the cut-off interval selected, we found enormous variation in the rate of POI ranging from 2% for a cut-off of 7 days and 60% for a cut-off of 1 day [17].

A physiological study, published in 1990, concluded that gastric motility recovered within 24—48 hours, small intestinal motility within 12—24 hours, and colonic motility in 3—5 days [23]. Advances in management have probably reduced these physiological durations since several teams have reported a median ROT (using the endpoint of Van Bree et al. [22]) of 24—48 hours.

Risk factors

Several risk factors have been identified in the literature but the studies are not reproducible for the reasons cited above. In fact, the low reliability of the data does not allow this problem to be effectively addressed. Table 1 reports the various reported risk factors, and the definition of ''normal'' interval to ROT used for data analysis. Despite this lack of reproducibility, various authors have repeatedly identified several risk factors, such as male gender, advanced age or significant blood loss [4,5,7,9,10].

Similarly, ROT is affected by the surgical approach, i.e., decreased for laparoscopy compared to laparotomy [24,25]. However, ''hand-assisted'' laparoscopy and robotic surgery do not appear to provide similar benefit compared

Table 1 Risk factors in relation to various definitions of POI.

Authors	Year	Type of surgery	Study design (# of patients)	Cut off time for POI (days); definition	Risk factors (OR or *P*-value)
Artinyan et al. [8]	2008	Abdominal surgery	Retrospective ($n = 88$)	6 days Intolerance to feeding	Blood loss ($P = 0.021$), opioid dosage ($P = 0.031$)
Svatek et al. [6]	2010	Radical cystectomy	Retrospective ($n = 283$)	6 days Absence of intestinal function Vomiting after a period of dietary tolerance	Advanced age (1.09), elevated BMI (1.09)
Kronberg et al. [86]	2011	Laparoscopic colectomy	Retrospective ($n = 413$)	5 days Absence of intestinal function or need for NG tube for abdominal distention, nausea, or vomiting	Narcotic use (3.17), previous abdominal surgery (2.41)
Kim et al. [11]	2011	Urologic surgery by laparoscopy	Retrospective ($n = 249$)	6 days Intolerance to solid feeding ± Abdominal distention ± Radiologic signs of ileus by abdominal plain X-ray	Dindo/Clavien score (5.3)
Millan et al. [9]	2012	Colorectal cancer surgery	Retrospective ($n = 773$)	6 days Absence of flatus with or without intolerance to feeding	Male sex (1.6), COPD (1.9) Stoma creation (1.9)
Vather et al. [10]	2013	Colorectal surgery	Retrospective ($n = 255$)	4 days POI definition of Vather et al. [10]	Advanced age (1.032), blood loss (1.943)
Chapuis et al. [4]	2013	Colon surgery	Retrospective ($n = 2400$)	3 days Abdominal distention + Absence of bowel sounds + Nausea and vomiting + No passage of flatus or stool	Male sex (1.7) PAOD (1.8) Respiratory comorbidity (1.6), emergency surgery (2.2) Perioperative transfusion (1.6), stoma formation (1.4), operative time exceeding 3 hours (1.6)
Vather et al. [7]	2015	Colorectal surgery	Prospective ($n = 327$)	4 days POI as defined by Vather et al. [10]	Male sex (3.1), low preoperative albumin level (1.11) Laparotomy approach (6.37) Increased size of incision Blood transfusion (1.84), volume of IV crystalloid infusion (1.55)
Moghadamyeghaneh et al. [5]	2015	Colon surgery	Retrospective ($n = 27{,}560$)	7 days No return of intestinal function	Ileocolic anastomosis (1.25), intra-abdominal infection (2.56), anastomotic leak (1.25), preoperative sepsis (1.63), carcinomatosis (1.24), COPD (1.27)

POI: postoperative ileus; COPD: chronic obstructive pulmonary disease; PAOD: peripheral arterial occlusive disease; BMI: body mass index.

to standard laparoscopic surgery. In addition, the retroperitoneal approach also helps to reduce POI; for abdominal aortic surgery, the risk of POI is decreased fivefold (odds ratio = 0.17; $P < 0.0001$) for the retroperitoneal approach compared to laparotomy [26].

Similarly, the risk of ileus depends on the type of surgery: the rate of POI for colorectal surgery is 10—30% [4—11] versus 8—13% after pancreatic and gastric surgery [27].

Other risk factors such as high-grade complications (on the Dindo-Clavien scale), intra-abdominal infection, or

anastomotic fistula are often reported [5,11], but should probably be classified as secondary POI.

Because most of the studies are retrospective and do not specifically focus on the role of morphine, opioids have not been commonly reported as risk factors for POI. However, prospective or retrospective studies that specifically evaluate morphine have highlighted its role in aggravating the risk of POI (OR = 12.1) [28]; opioids have a dose-dependent inhibitory effect on intestinal motility [28—30]. In addition, morphine aggravates the consequences of POI and increases the duration of hospitalization [29].

Risk factors that have been more anecdotally identified include a history of prior laparotomy, the length of the abdominal incision [29—32], and emergency surgery (with associated major intestinal edema) [33].

Pathophysiology

While the lack of consensus regarding the normal duration of POI causes confusion and non-reproducibility of studies, progress in basic science could help to advance understanding of the pathophysiology of POI, thereby helping to prevent and cure this complication.

POI arises from autonomic nervous and hormonal mechanisms. Its origin is multifactorial since intestinal manipulation, administration of opioid or anxiolytic medications, and postoperative stress all seem to be involved in the initiation of POI.

However, most experimental studies on the mechanism of POI have dealt with murine models, which are only partially superimposable to man.

POI develops in three phases. The initial phase involves neurological processes (via the sympathetic nervous system), while a second phase involves hormonal and inflammatory mechanisms. Finally, a third phase involves parasympathetic nervous activation, which plays a major role in the resolution of ileus (anti-inflammatory role).

Neurological phase

The first phase of ileus involves sympathetic nervous system pathways. Anesthesia and the surgical incision induce the activation of presynaptic noradrenergic B receptors (AF I think these are called ''presynaptic beta-adrenoceptors'' they are beta even in French!), however, manipulation of the intestine does not appear to involve this pathway [34].

These fibers act on the enteric nervous system (ENS) and the sympathetic nerves. The connections between these two entities are not yet identified. Furthermore, within the ENS, glial cell dysfunction could lead to dysequilibrium of the intestinal mucosal barrier [35].

Stimulation of alpha-2 adrenergic receptors in the inflamed muscularis mucosae could play a role in aggravating ileus by increasing the synthesis of messenger RNA of the inducible nitric oxide synthetase (iNOS mRNA) with release of nitrogen monoxide (NO) [36]. An increase in NO causes activation of CycloOxygenase-2 (COX2). This has raised the question of whether NSAID drugs could be useful to improve ROT (but there is a corresponding possibility that they also impair wound healing, leading to an increased rate of anastomotic leaks) [37—41].

Inflammatory phase and intestinal manipulation

As the neurological phase fades, increased inflammation is noted in the walls of the intestine, involving monocytes, macrophages and mast cells that secrete pro-inflammatory molecules and autoregulate themselves.

Manipulation of the intestines induces an inflammatory response in the 3rd hour of a laparotomy intervention. This inflammation is not observed with the laparoscopic approach [42], which may explain some of the beneficial effect of this surgical approach in preventing POI. Manipulation activates dendritic cells that produce interleukin 12 (IL) [43]. IL adheres to T1 helper lymphocytes (T1H) that then migrate to non-manipulated sites and induce inflammation in these remote areas by secreting alpha interferon (IFN alpha), which, in turn, recruits macrophages. This is called the ''field effect'' [43]. This dissemination of inflammation could explain how a drain that creates localized inflammation in the pouch of Douglas may result in prolongation of POI in the entire digestive tract.

During this second phase, the permeability of the intestinal epithelial barrier is increased, resulting in bacterial translocation, which could also increase inflammation and POI [42].

Furthermore, variations in potassium concentration may play a role in POI by opening calcium channels [44]. These last two items explain the role of fluid and electrolyte over-replacement in the pathogenesis of POI and thus, the potential benefits of reducing crystalloid replacement to maintain optimal ''natural'' homeostasis.

Phase of resolution of ileus and vagal activation

Increased vagal tone reduces the inflammation induced by intestinal manipulation. This is mediated through nicotinic alpha 7 acetylcholine receptors (alpha7-nAChR) and 5-hydroxytryptamine 4 receptors (5-HT4R). Activation of 5-HT4R results in increased acetylcholine release by the myenteric cholinergic neurons. This allows activation of alpha7-nAChR on monocytes and macrophages and thereby reduces the inflammatory response [45].

This last so-called ''resolution'' phase is mediated by the vagal system, and could explain the positive effect of gum chewing or early mobilization (prehabilitation) that stimulate the vagal system and thereby reduce POI [46].

Treatments

With knowledge of the different risk factors and progressive understanding of the pathophysiology of POI, ERAS protocols have grouped together a variety of therapeutic measures, with the aim, among other goals, of preventing POI.

These measures target the different phases of ileus and upcoming subchapters connect each preventive measure to the pathophysiology.

Alvimopan

Alvimopan is an antagonist of the μ opioid receptor; its efficacy has been evaluated several times including in randomized studies. Alvimopan is not currently available in France. It acts essentially on phase 1 of ileus, opposing the

muscle relaxant effects of opioids. Recent literature suggests that use of alvimopan shortens the interval to ROT [47]. The effectiveness is more marked when patients are receiving analgesic doses of morphine [48]. A 2012 meta-analysis confirmed that alvimopan is beneficial in decreasing POI but noted that the beneficial effect has not yet been confirmed for laparoscopic surgery [49].

Lidocaine

Intravenous infusion of lidocaine works on phase 1 of POI by reducing pain and therefore sympathetic stimulation. Some ERAS protocols have recently introduced intravenous lidocaine as a therapeutic measure. Its effect on improving ROT has recently been demonstrated (decrease in risk of POI with an OR = 0.38), but current ERAS protocols are not consensual and two recent meta-analyzes have pointed out the inadequate documentation of side effects and that there is no consensus for the protocols for lidocaine infusion [50,51].

Propranolol

Propranolol, a beta-blocker agent that acts on beta-adrenergic fibers, was evaluated in a randomized controlled trial that was unable to show any effect on intestinal myoelectric activity [52].

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs act on phase 2 of ileus and are intended to reduce postoperative inflammation by their action on COX2 (as well as COX1 for non-specific NSAIDs). While NSAIDs have a promising theoretical mode of action on the pathophysiology of POI, some authors have decried their use after colorectal resection, particularly because they attribute an increased risk of postoperative anastomotic leak (AL) to them [37,38]. However, NSAIDs have a clear beneficial effect on ROT [39] while the increased risk of AL remains debated [41]. A recent review of the literature concluded that short (48 h) treatment with NSAIDs after colorectal surgery could be recommended [40].

Pro-kinetic agents: magnesium-gastrografin

Many prokinetic have been evaluated in literature.

Intravenous magnesium

Intravenous magnesium was studied in a randomized controlled trial that demonstrated a decrease in the interval to ROT without any side effects [53]. Magnesium sulfate was administered as a bolus of 40 mg/kg, followed by an infusion of 10 mg/kg during the operative period.

Metoclopramide

Metoclopramide has been little studied with regard to its effect on ROT. While an initial study showed no effect on gastrointestinal function [54], a more recent study showed more rapid ROT following gastrectomy and intraperitoneal chemotherapy [55].

Choline citrate

A single randomized controlled trial concerning choline citrate found no effect on ROT [56].

Mosapride citrate

Mosapride citrate may have a beneficial effect on the rate of ileus by increasing gastric and duodenal muscular contraction and reducing the interval to ROT. However, only one study with a small number of patients has investigated this effect [57].

Erythromycin

Two randomized controlled trials have studied oral erythromycin after colonic and gastric surgery and were unable to show any beneficial effect on ROT [58,59].

Gastrografin

Gastrografin has been studied in two recent randomized controlled trials and, although it did not significantly reduce the duration of POI [60,61], it may have reduced the duration of nasogastric suction [60]. Moreover, gastrografin has clinical benefits by shortening the interval to passage of flatus and stool and by reducing abdominal bloating [61].

In 2008, a Cochrane meta-analysis studied many prokinetic agents and could not identify any beneficial effect on ROT [62]. Magnesium was not evaluated in this meta-analysis. Alvimopan was evaluated but the authors concluded that despite the existence of several studies reporting a beneficial effect, there were too many methodological biases and that alvimopan must still be considered experimental.

Prevention

Epidural analgesia

Although highly recommended to improve pain control after laparotomy, the role of epidural analgesia in the era of laparoscopic surgery is debatable. Recent studies have not been able to show any benefit associated with the use of epidural analgesia after laparoscopic colorectal surgery [63,64]. These results, however, are open to debate since the definition of POI was variable for each author.

Surgical approach

The main mechanism of POI involves phase 2, particularly the inflammatory response to bowel manipulation. We have previously reported that laparoscopy did not induce inflammation related to intestinal manipulation. The clinical literature has also reported improvement in gastrointestinal motility related to the use of the laparoscopic approach, particularly for colorectal and gallbladder surgery [65,66]. A recent prospective randomized controlled study showed that a laparoscopic approach was associated with a 30% decrease in POI after colectomy for diverticulitis [66].

Nicotine gum and chewing gum

Mastication of chewing gum mimics dietary intake. Chewing stimulates vagal tone, which has an anti-inflammatory effect (phase 3 of ileus). Use of chewing gum has been discussed in the literature with regard to all surgical specialties.

The most significant studies report an improvement in the interval to ROT [67,68]. Its efficacy in pancreatic surgery has not been proven statistically although there was a decreasing interval to ROT [69]. While most studies agree

that gum chewing improves gastrointestinal function, a consensual protocol has not been defined. In most studies, patients were instructed to chew gum 3—4 times daily for 5 to 45 minutes [68].

Nicotine chewing gum could have a favorable effect on ROT because of its anti-inflammatory effect (anti-TNF, fewer macrophages...) [70].

Finally, it seems that the beneficial effect is greater if gum chewing is started preoperatively. A recent randomized controlled study highlighted improved ROT in this group, along with a decrease in inflammation (reduction of IL 8 and TNF alpha) [71].

Early resumption of diet

Early feeding decreases the risk of infectious complications, protein wasting, and leaky intestinal mucosa [72]. It also reduces the need for IV hydration and potential electrolyte imbalance [72]. Reducing the volume of IV fluids reduces the incidence of POI [73].

Early resumption of diet significantly reduces the duration of ileus after major rectal surgery [74] and is feasible, even after emergency surgery [75].

Coffee

The mechanism of coffee's effect is not currently known. The first randomized controlled trial noted an improvement in gastrointestinal function when patients drank coffee without worsening of postoperative morbidity [76]. In a more recent study, decaffeinated coffee was shown to have the same efficacy [77].

Dai-Kenchu-To (DKT)

DKT is a Japanese herbal remedy that is widely used in traditional medicine. Its anti-inflammatory effect is mediated by the alpha-7nACh receptor (phase 3). Several studies have shown an improvement in the interval to ROT with the use of this herb [78,79].

Experimental agents

Parenteral administration of polyunsaturated fats may have a positive effect on ROT [80].

Enhanced recovery programs

The principles of enhanced recovery programs are now well known. It was reintroduced by Scandinavian teams, including the ERAS Society, which first published recommendations particularly for colorectal surgery [18,19], with the intent of decreasing perioperative stress. Enhanced recovery programs now include most of the above-mentioned measures in order to optimize perioperative management.

Enhanced recovery programs have successfully reduced the duration of hospital stay and recovery time after surgery, while reducing (or at least not increasing) perioperative morbidity [81,82]. Some enhanced recovery programs have also demonstrated improvement in the interval to ROT [17,83—85] and reduced the rate of POI [81]. Thus, compliance with at least 85% of the measures in an enhanced recovery program has been shown to reduce the risk of prolonged (> 4 days) POI (OR = 0.35) [17].

Regarding the resumption of global transit, a meta-analysis by Zhao et al. showed that enhanced recovery programs reduced the interval for passage of flatus by 0.4 days [81] and, in a second meta-analysis, that the laparoscopic approach was of major interest for ROT in enhanced recovery protocols since it decreased the interval to the first bowel movement by 1.1 days ($P < 0.001$) [82].

Most of the work on these programs has been made in the context of colorectal surgery but protocols are available for other surgical specialties on the web sites of the ERAS Society and GRACE Association [12,13]. The effect of enhanced recovery protocols on gastrointestinal recovery in other specialties has not yet been demonstrated.

Conclusion

POI is a complex phenomenon that occurs very commonly and impacts on several surgical specialties. Its mechanism is only partially understood, but several measures have already been proposed that have enabled a significant reduction in the duration and frequency of POI [86]. Most of these measures have been effectively incorporated into enhanced recovery programs.

One of the obstacles to improving the fight against POI is the lack of consensus on its definition, making the literature non comparable. While the majority of measures aim more at the prevention of POI than its treatment, it is logical to think that, just as with gum chewing, patient ''prehabilitation'' could improve the effectiveness of prevention.

Much progress has been made in the fight against POI, but much more remains to be done, especially in the introduction of the concept of ''prehabilitation'' in enhanced recovery protocols.

Disclosure of interest

The authors declare that they have no competing interest.

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X. Discussion générale

Cette thèse, à l'interface entre recherche clinique et translationnelle, a permis des avancées à la fois cliniques et physiopathologiques tout en identifiant de nouvelles méthodes thérapeutiques d'intérêt.

A partir de constatations cliniques, nous avons pu réaliser une étude fondamentale sur les mécanismes de l'IPO dans le côlon chez les patients suivant un programme de réhabilitation améliorée (« from bedside to bench »). Si il était connu que la COX-2 était impliquée dans l'iléus postopératoire chez l'Homme (87), nous avons pu montrer que l'ARNm de cette enzyme était moins exprimée dans la paroi du côlon des patients suivant un programme de réhabilitation améliorée par rapport à ceux n'en suivant pas. Parallèlement, nous montrions une diminution de l'expression des ARNm de COX1 mPGES1 et de HPGDS.

Toutefois, malgré la réhabilitation améliorée et la diminution de l'expression des *ARNm* de ces différentes enzymes, le délai de récupération des fonctions gastro-intestinales restait corrélé à HPGDS et l'inhibition pharmacologique de mPGES1 avait un effet favorable sur la motricité ex-vivo du muscle circulaire lisse colique. Ceci explique pourquoi les anti-inflammatoires non stéroïdiens (AINS) systémiques ont un effet favorable sur la reprise du transit (inhibition de la voie des COX ou de la voie de COX-2 selon le caractère sélectif de l'AINS). D'ailleurs, certains auteurs proposent l'utilisation systématique de protocoles courts d'anti-inflammatoires dans la période postopératoire immédiate (133) mais l'innocuité de ce traitement, notamment sur les fistules n'a pas pu être établi (165,166) et certains auteurs ne recommandent pas leur utilisation (166). En effet, une inhibition plus ciblée de mPGES1 permettrait d'inhiber la synthèse de PGE2 qui a des effets ralentisseurs du transit (91,92), sans inhiber la synthèse de PGD2 qui a

des effets pro-kinétiques (94), ou 15d-PGJ2 et PGI2 qui ont des effets anti-inflammatoires (167,168).

L'inhibition spécifique de mPGES1 n'est à ce jour pas possible dans la pratique clinique mais des essais de phase 2 ont pu montrer qu'il existe un effet moins délétère de cet AINS sur le rein par rapport aux AINS classiques (169). Par ailleurs, nous avons pu mettre en évidence une amélioration de la fonction motrice intestinale ex-vivo par le biais de l'inhibition de la mPGES1. Ainsi, cette inhibition spécifique s'avère être une voie thérapeutique ou de prévention à favoriser par le biais de mesures médicamenteuses et instrumentales. Cependant, les effets secondaires cliniques, notamment sur la cicatrisation restent à déterminer car la PGE2 est rapportée comme pro-cicatrisante (170) et son inhibition complète pourrait avoir des risques anastomotiques. C'est pour cette raison que nous avons développé le modèle murin d'iléus. Celui-ci permettra de mettre en évidence des cibles thérapeutiques de l'iléus qui pourront être validées par la mise en place d'études cliniques.

Par exemple, parallèlement à ce modèle préclinique, et afin de confirmer le rôle central de la mPGES1 dans la physiopathologie de l'IPO, nous avons développé une première étude clinique de faisabilité de la stimulation tibiale postérieure percutanée périopératoire. Le rationnel de cette étude reposait sur le fait que nos travaux fondamentaux mettaient en évidence un rôle majeur des médiateurs lipidiques de l'inflammation dans la physiopathologie de l'IPO au niveau colique (Frome « Bench to Bedside »), et sur le fait que la neuromodulation sacrée à un effet anti-inflammatoire sur le côlon et le rectum (160). Stimuler le tube digestif terminal dans la RA, semble d'intérêt car il ne possède pas ou peu de terminaisons vagales alors que l'effet anti-inflammatoire emprunte essentiellement la voie vagale et a donc un effet

essentiellement au niveau de l'intestin grêle. Boeckstaens *et al*. (158) ont par ailleurs récemment mis en évidence un effet protecteur de l'iléus par le biais d'une stimulation vagale électrique sur un modèle murin.

Malgré un nombre limité de patients inclus, nous avons pu mettre en évidence une diminution significative du nombre des iléus chez les patients stimulés par rapport aux patients non stimulés. Bien que cette diminution soit probablement en partie liée au petit nombre de patients inclus, il n'en demeure pas moins que les ARNm des différentes enzymes de la chaine de AA, et notamment la mPGES1, suivaient la même tendance, en étant moins exprimées dans le groupe de patients stimulés. Cette information renforce donc le rôle central de a mPGES1 dans la physiopathologie de l'IPO et comme cible thérapeutique. L'addition de cette thérapeutique instrumentale aux programmes de réhabilitation améliorée pourrait donc permettre une amélioration des suites opératoires mais ne permettra malheureusement probablement pas d'éradiquer complètement cette morbidité opératoire.

Notre travail présente toutefois quelques limitations inhérentes à la complexité des mécanismes physiopathologiques. En effet, du fait des multiples facteurs intervenant dans l'iléus, il peut être erroné de conclure à l'effet privilégié d'un facteur particulier. Ainsi, bien que significatives, les corrélations obtenues dans l'article 6 étaient faibles. Par ailleurs, il est difficile d'étudier les effets de la RA qui sont souvent confondus par les effets de la coelioscopie. En effet, la coelioscopie permet une diminution connue de l'inflammation et est difficilement dissociable des programmes de RA.

Enfin, sur le plan du modèle murin, il reste à définir si la physiopathologie de l'IPO chez l'animal est superposable à celle de l'être humain. Par ailleurs, ce modèle ne permet de se superposer à la RA puisque nous n'avons pas développé le modèle coelioscopique.

Cependant, nos études des mécanismes ont permis d'aboutir à des études de nouvelles voies thérapeutiques efficaces, encourageant la poursuite de nos travaux dans ce sens.

XI. Conclusion

Notre travail a donc permis d'identifier la voie du métabolisme de l'acide arachidonique comme potentiellement impliquée dans l'iléus postopératoire. Cette voie pourrait être ciblée afin d'améliorer la prise en charge thérapeutique de l'IPO. Toutefois leur impact direct reste à identifier.

Ces voies représentent donc non seulement des nouvelles cibles thérapeutiques mais aussi des biomarqueurs prédictifs d'IPO pouvant cibler les patients à prendre en charge. Un challenge actuel vise à développer des approches permettant de cibler tout le long du tube digestif ces dérivés lipidiques et nécessite probablement le développement d'approches combinées de prise en charge médicamenteuse, nutritionnelle et instrumentale.

A terme, ceci pourrait permettre de réduire de manière significative le surcoût lié à l'IPO estimé à plusieurs dizaines de millions d'euros et également l'impact sur la qualité de vie des patients.

XII. Bibliographie

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UNIVERSITE BRETAGNE LOIRE

UNIVERSITÉ DE NANTES

Thèse de Doctorat

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ILEUS POSTOPERATOIRE : Mécanismes et Prévention

POSTOPERATIVE ILEUS : Mechanism and prevention

Résumé

L'iléus postopératoire (IPO) représente la complication la plus fréquente après chirurgie colorectale (20-30%). Ses conséquences sont importantes tant à l'échelle médico-économique qu'à l'échelle individuelle, puisqu'elle impacte sur le confort du patient et peut également être liée à des complications sévères. Bien que les programmes de réhabilitation améliorée (RA) aient permis de réduire l'incidence de l'IPO, ils pourraient être optimisés en améliorant nos connaissances dans les mécanismes physiopathologiques menant à l'IPO, notamment dans le colon.
Ce travail s'inscrit dans cet objectif général et vise 1) à mieux comprendre le rôle des médiateurs d'origine lipidique dans l'IPO et 2) à tester de nouvelles voies thérapeutiques ou préventives.
D'une part, nous avons montré que la RA diminuait l'expression des enzymes de la chaine de dégradation de l'acide arachidonique (AA). Néanmoins, l'*ARNm* de HPGDS et mPGES1 restaient associés à la durée de reprise du transit. D'autre part, nous avons montré que la stimulation tibiale postérieure percutanée diminuait l'incidence de l'IPO et que ses effets étaient liés notamment à une diminution de l'*ARNm* mPGES1.
Nos travaux identifient donc la voie de l'AA comme acteur de l'IPO colique. De plus, ces voies représentent une cible prometteuse par approche nutritionnelle ou instrumentale.

Mots clés
Ileus postopératoire, prévention, chirurgie colorectale, inflammation, mPGES1, médiateurs lipidiques

Abstract

Postoperative ileus (POI) is the most important complication after colorectal surgery (20-30%). Consequences are important as much as a medico-economic level as at an individual level because it impacts on the comfort of patients in postoperative course and because it can also be linked to severe morbidity. While enhanced recovery programs (ERPs) allowed a reduction of POI, it could be optimized, improving our knowledge on the pathophysiologic mechanisms leading to POI, especially in the colon.
This work has this general objectives and aims 1) to better understand the role of lipid mediators in POI and 2) to test new preventive or therapeutic pathways.
In one hand, we showed that ERPs reduced the expression of enzymes of the arachidonic acid (AA) metabolism. However, HPGDS and mPGES1 *mRNA* remained associated to the delay for gastrointestinal function recovery. In the other hand, we showed that percutaneous tibial posterior nerve stimulation reduced the incidence of POI and that its effects are especially due to a reduction of mPGES1 *mRNA*.
Our works identify the AA pathway as the actor of colonic POI. Furthermore, these pathways are a promising target by nutritional or instrumental approach.

Key Words
Postoperative ileus, prevention, colorectal surgery, inflammation, mPGES1, lipidic mediators

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