Updates in Surgery (2019) 71:17–20
https://doi.org/10.1007/s13304-019-00627-2

REVIEW ARTICLE

Hyponatremia could identify patients with intrabdominal sepsis and anastomotic leak after colorectal surgery: a systematic review of the literature

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Received: 28 November 2018 / Accepted: 27 January 2019 / Published online: 8 February 2019

Abstract
Anastomotic leak (AL) is a serious post-operative complication in colorectal surgery. It can lead to devastating morbidity and mortality. Clinicians usually depend on a combination of clinical, biochemical and radiological findings to diagnose this problem. In our article, we tried to look if electrolyte disturbances could be indicators for intra-abdominal sepsis due to AL. Systematic review of the literature identifies a potential correlation between electrolyte alterations and AL in digestive surgery. The following databases were searched: PubMed, EMBASE and MIDLINE. The review adhered to the PRISMA statement for systematic review. Our literature search did not identify any articles linking any electrolyte disturbances—except for hyponatremia—to AL. Pathophysiology of these electrolyte disturbances does not seem to be linked to AL, except for hyponatremia which might be explained. Our review included 442 patients with intra-abdominal sepsis and 1133 controls. The mean specificity of hyponatremia being associated with intra-abdominal sepsis is 86%, whereas mean sensitivity is 28%. Hyponatremia seems to be a significant and clinically relevant marker for of intra-abdominal sepsis and AL.

Keywords Anastomotic leak · Hyponatremia · Electrolyte disturbance · Colorectal surgery · Complication

Introduction

Anastomotic leak (AL) is a major complication in colorectal surgery, which could be life-threatening. Despite improvements in surgical technique and peri-operative care, AL still occur, and with them occur increased morbidity, mortality, length of stay, and costs [1, 2]. Surgeons usually depend on a combination of clinical, biochemical and radiological findings to early diagnose this problem. It is well known that inflammatory markers such as leucocytes and C-reactive protein (CRP) counts post-operatively are useful tools to pick up this complication. Clinicians sometimes rely on CT with rectal enema to surely identify AL.

Electrolyte disturbances have been correlated with AL. As an example, low sodium levels have been linked in the literature as a strong predictor of AL, which seems to be increased for values below 136 mmol/l [3]. However, the values for sensitivity and specificity of electrolyte disturbances for AL vary significantly in published studies.

Aim of this study is to review the literature for articles that looked into electrolyte disturbances as possible markers for primary intrabdominal sepsis and AL, to define the

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association between the events, and the possible pathophysiology leading to AL.

Materials and methods

A systematic review was performed in accordance with the PRISMA guidelines (Fig. 1) [4]. We reviewed literature using PubMed, EMBASE and MIDLINE databases.

The following keywords were used included: "electrolyte disturbance", "hyponatremia", "hypernatremia", "hypokalemia", "hyperkaliemia", "hypercalcaemia", "hypocalcaemia", "hypermagnesemia", "hypomagnesaemia", combined with "anastomotic leak", "intraabdominal sepsis", "peritonitis".

We searched articles in the period between 1960 and 2018, including English-only articles. The search included all forms of study designs (i.e. case–controls, cohorts and descriptive studies).

The initial search did not return any articles describing electrolyte disturbances (i.e. hypernatremia, hyperkaliemia, hypokalemia, hypercalcaemia, hypocalcaemia, hypermagnesemia, hypomagnesaemia) in relation to AL or abdominal sepsis. We only identified hyponatremia as a possible indicator for AL after colorectal surgery. Therefore, we decided to focus on hyponatremia only.

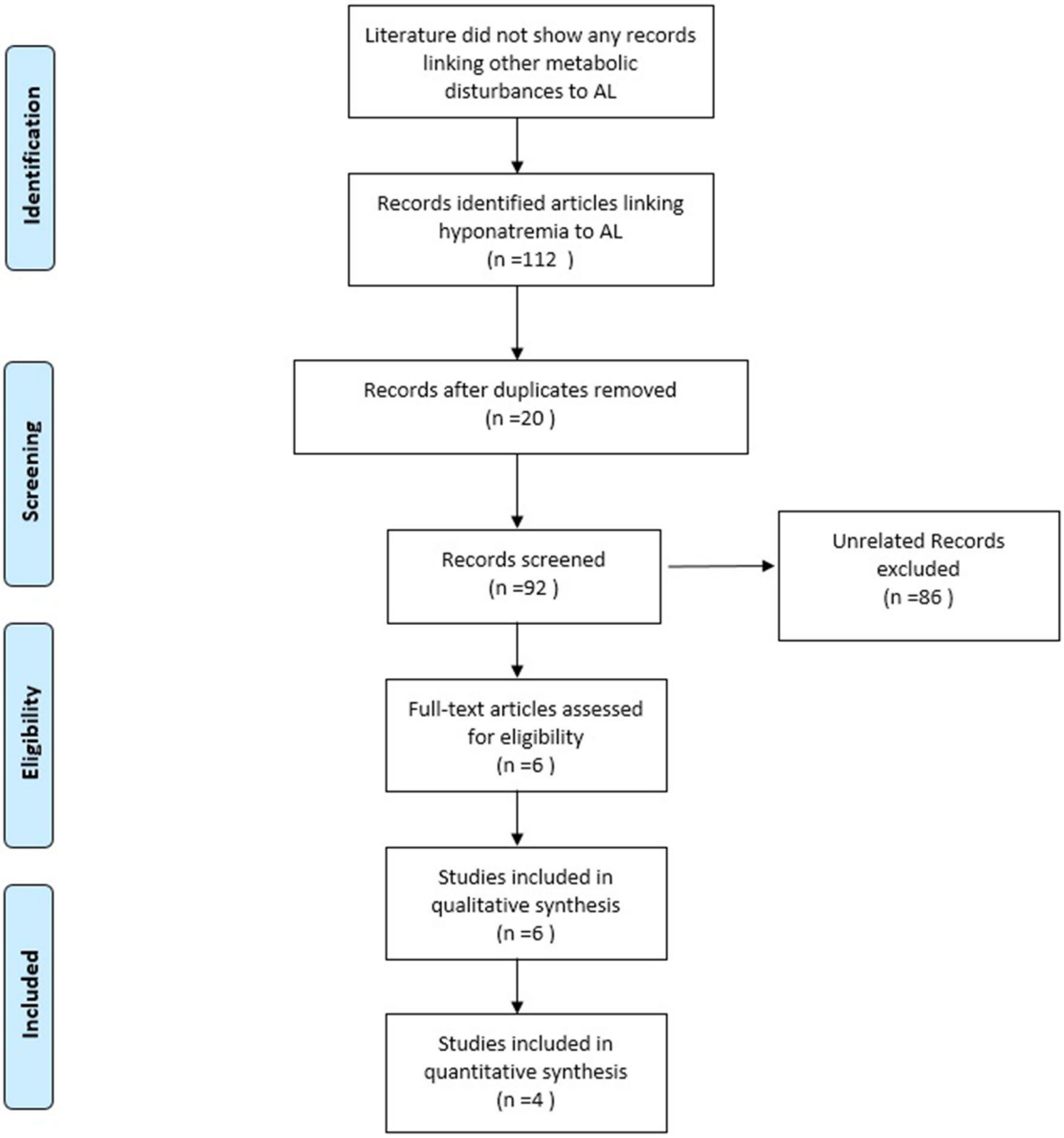

Fig. 1 PRISMA algorithm breakdown for the selection of relevant papers

The primary aim was to identify the potential correlation between hyponatremia and primary intrabdominal sepsis or AL in patients who underwent colorectal surgery. Only article assessing patients who developed AL after colorectal surgery or primary intrabdominal sepsis was evaluated for inclusion, and included if they assessed the role of hyponatremia. During our analysis, we converged all the results to represent them as mean percentage for the association.

For the secondary aim, we revised the literature to identify the pathophysiological mechanisms underlying the association between hyponatremia and AL.

Results

Overall, we reviewed 102 articles; 20 were excluded as duplicates, 86 articles were excluded as they were unrelated. Four retrospective clinical studies were included.

In total, we identified 442 patients with AL or abdominal sepsis/peritonitis and 1133 controls.

In their prospective study on consecutive patients operated between 2007 and 2012, Kaser et al. [3] included 81 patients with AL and 1025 controls. AL was confirmed by CT with water-soluble contrast, proctoscopy, or obvious leakage in the drains. The sensitivity for hyponatremia was 24%, whereas specificity was 93%.

Clowes et al., included 25 patients who developed peritonitis, who were observed in two hospitals in US in 1966. There were different causes for peritonitis, but mainly due to perforated viscus. They suggested a sensitivity of hyponatremia of 25% and specificity of 95% [5].

Another study included 282 patients with colonic perforation—either for diverticulitis or appendicitis. This was a retrospective study in Switzerland in the period between Jan 2008 and Dec 2010. All consecutive patients above 50 years with perforated diverticulitis or appendicitis were included. The presence of perforation was confirmed by CT scan or by surgical exploration. Sensitivity of hyponatremia in these cases was 31%, whereas specificity was 79% [6].

In a retrospective case–control study from Spain, Serradilla et al., observed 54 cases of intra-abdominal sepsis secondary to perforated appendicitis and 108 controls between 2011 and 2016. The main variable was the presence of intra-abdominal abscess post-gangrenous appendectomy [7]. Hyponatremia was sensitive in 32% and specific in 78%.

We calculated the mean sensitivity and specificity of hyponatremia in cases of AL or colonic perforation. The mean specificity of hyponatremia being associated with intra-abdominal sepsis is 86%, whereas mean sensitivity is 28%.

Discussion

Electrolytes including Na represents routine blood test that is usually done in all patients scheduled for colorectal surgery and in the post-operative phase. Hyponatremia on post-operative days 5–7 in patients who are unwell can raise the suspicion of a AL. Nutritional status assessed with albumin and other metabolic factors have been advocated as concurrent determinants of AL after colorectal resections [8, 9]. Our review did not identify other electrolyte disturbances apart from hyponatremia as indicators for intra-abdominal sepsis. Their pathophysiology is not clearly understood in this association.

From the previous retrospective analysis, we conclude that hyponatremia has high specificity profile for AL. Authors suggested that, if combined with both leukocytosis, hyponatremia can have a specificity of 98% for AL [3].

Due to low sensitivity (28%), the absence of hyponatremia cannot be used to exclude AL after colorectal surgery.

Hyponatremia is associated with intra-abdominal sepsis. It can be associated with perforated appendicitis, perforated diverticulitis, and AL. These complications apparently share the same pathophysiology, which induces acute stress and results in intra-abdominal sepsis.

Hyponatremia is correlated significantly with colonic perforation. This is of certain clinical importance, if considering that sodium measurement costs much less than measurement of CRP or other inflammation markers. Moreover, sodium is often measured in the daily routine [6].

The use of CT with rectal contrast alone to diagnose AL raises the risk of false-negative cases [10]. Also, lower two-third rectal anastomosis with a diverting loop ileostomy may have subtle symptoms. The reported biochemical markers can help clinicians to suspect AL irrespective of the presence of a diverting stoma. An AL in defunctioned patients usually has a delayed diagnosis [3].

There are different theories linking hyponatremia to AL. AL is a significant stress to human body. As a result, cytokines and acute-phase proteins including IL-6, IL-1β and TNF-α are secreted. IL-6 crosses blood–brain barrier leading to non-osmotic secretion of vasopressin form posterior pituitary through neurons of supraoptic nucleus (SON) and paraventricular nucleus (PVN). This will switch on the immune–neuroendocrine interface represented by IL-6 signaling. This complex binds to gp 130, which leads to dimerization of two molecules. These are "intracellular janus kinases" (JAK) and "signal transducer and activators of transcription" (STAT) protein. This activation stimulates ADH, which eventually leads to water retention resulting in hyponatremia [11, 12]. This mechanism could justify our findings.

Table 1 Patients included in each study and sensitivity/specificity values for hyponatremia and intra-abdominal sepsis

Study	Intra-abdominal sepsis	Controls	Sensitivity (%)	Specificity (%)
Clowes (1966)	25	–	25	95
Kaser (2013)	282	–	31	79
Kaser (2014)	81	1025	24	93
Serradilla (2018)	54	108	32	78
Overall	442	1133	28 (mean)	86 (mean)

Our findings should be considered with caution, due to the quality of the included studies and to the paucity of data. In addition, AL is a multifactorial event, as well as many factors are implied in intra-abdominal sepsis. However, it should be noted that no agreed, specific clinical signs and laboratory tests exist to reject or confirm the diagnosis of post-operative peritonitis [13]. Therefore, investigating further the role of hyponatremia as a marker of post-operative abdominal septic could be of value (Table 1).

Hyponatremia seems to be a significant and clinically relevant marker of intra-abdominal sepsis and could be used to identify patients with AL after colorectal surgery. The absence of hyponatraemia does not rule out AL. Future studies are required to demonstrate any link of other electrolyte disturbances to intra-abdominal sepsis.

Acknowledgements The authors wish to thank the Royal Marsden Hospital Biomedical Research Council (BRC) for their support.

Funding All Authors have no source of funding.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

Research involving human participants and/or animals This article did not involve human participants and/or animals.

Informed consent No procedures were conducted by the authors on patients; there was no need of informed consent. This review was in agreement with the Good Clinical Practice.

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