ACUTE ABDOMINAL PAIN: FROM ASSESSMENT TO MANAGEMENT
A registry analysis and a meta-analysis

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Ph.D. dissertation

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2. **Földi M**, Soós A, Hegyi P, Kiss S, Szakács Z, Solymár M, Pétervári E, Balaskó M, Krzysztof K, Molnár Zs. Transversus Abdominis Plane Block Appears to Be Effective and Safe as a Part of Multimodal Analgesia in Bariatric Surgery: A Meta-analysis and Systematic Review of Randomized Controlled Trials. Obesity Surgery. 2021;31(2):531-43. **(Q1, IF: 3.479))**

LIST OF ABBREVIATIONS

IASP International Association for the Study of Pain

NRS Numerical Rating Scales

VAS Visual Analog Scales

NSAID Non-steroidal anti-inflammatory drugs

APS-POQ-R Revised American Pain Society Patient Outcome Questionnaire

AP Acute pancreatitis

APACHE-II Acute Physiology and Chronic Health Evaluation

EA Epidural analgesia

ERAS Enhanced Recovery After Surgery

TAP block Transversus abdominis plane block

USG Ultrasound guidance

RCTs Randomized controlled trials

HPSG Hungarian Pancreatic Study Group

LOS Length of hospital stay

BMI body mass index

CCI Charlson Comorbidity Index

PRISMA Preferred Reporting in Systematic Reviews and Meta-analyses

SD Standard deviation

CI Confidence Interval

IQR Interquartile range

OR Odds ratio

SHAM serious harm and morbidity

1. INTRODUCTION

The International Association for the Study of Pain (IASP) published the revised definition of pain in 2020: "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". We currently lack an objective pain assessment tool, only self-reporting questionnaires can be used. The most used methods to assess pain are the pain intensity scales that try to quantify the subjective experience, such as the Numerical Rating Scales (NRS) or Visual Analog Scales (VAS). They are quick to use, even in the emergency care. Particularly encouraging that a shift toward more complex assessment tools can be observed, for example the Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R) or International Pain Outcomes Questionnaire can be considered here.

Acute pancreatitis (AP) is the most common acute gastroenterological disorder that requires hospitalization, and is commonly presented with acute abdominal pain. Its mortality can be as high as 20% in severe cases.

Acute abdominal pain is among the diagnostic criteria of AP. Since the pain can be excruciating, adequate pain management is of the utmost importance. However, we currently lack specific guidelines for pain management in AP; instead, general perioperative strategies are recommended.

Early identification of patients at a higher risk of severe AP and mortality is essential for proper monitoring and management. The most frequently used prognostic scores, such as the Ranson score and APACHE-II (Acute Physiology and Chronic Health Evaluation), are difficult to follow, can be evaluated only after 72 hours of hospitalization, and are not sufficiently accurate, according to the limited evidence in the literature. These traditional prognostic scores do not address questions concerning pain or other clinical symptoms.

Recently a new score, the Pancreatitis Activity Scoring System has been proposed to provide an objective tool to evaluate disease activity. This score was found to be associated with clinical outcomes of AP. The interesting thing about the score is that pain intensity and the need for analgesia also play a role in addition to complications and feeding intolerance.

Also, identifying risk groups requiring special attention as regards pain management and to choose or even expand the available analgesics for them, thus providing personalized medicine is essential.

According to previous systematic reviews, only a few randomized clinical trials have investigated optimal pain management in AP. In addition, we need further descriptions of analgesic strategy in a real-world setting. There is an ongoing debate about non-steroid anti-inflammatory drugs (NSAIDs) vs opioids in AP. Non-pharmacological therapies have gained less attention such as epidural analgesia or ultrasound guided elector spinae plane block (ESPB).

Ideally, multiple analgesic modalities are applied. This concept is called multimodal analgesia. The ERAS (Enhanced Recovery After Surgery) guidelines used in perioperative care has long embraced this concept. ERAS guidelines, as the name implies, facilitate faster recovery after surgery. Besides multimodality, it also supports evidenced-based and patient-centered approaches.

Pain in the postoperative period can cause serious suffering to patients, prolong recovery, and increase healthcare costs. Although growing evidence supports multimodal analgesic techniques in clinical practice, opioids still remain among the first choice of postoperative pain management. Instead of opioids, NSAIDs and other pharmacological options (e.g. ketamine, gabapentin), or the locoregional analgesic techniques are among the alternatives in a postoperative setting. Infiltrative techniques—including *transversus abdominis plane block (TAP block)*—have gained increasing attention in recent years as they can be safely and efficiently applied. Many studies have been published about TAP block in different types of abdominal surgeries, including bariatric surgeries. Since the role of TAP block in bariatric surgery has not been properly defined by the existing randomized controlled trials (RCTs) with small sample sizes, no clear recommendation has been released by the ERAS society.

2. AIMS

2.1. Acute abdominal pain in AP – registry analysis

We aimed to identify clinical parameters that potentially influence pain intensity, type, localization, and duration prior to admission in AP. Also, we would like to elucidate the relationship between the characteristics of pain on admission and the main outcomes of AP

(possible prognostic role of pain). Finally, we described pain management in the everyday practice of AP care.

2.2. Acute abdominal pain after bariatric surgery – meta-analysis

We aimed to assess the effects of USG-TAP block as a part of multimodal analgesia for postoperative pain management in patients undergoing laparoscopic bariatric surgery

3. METHODS

3.1. Methods – "Acute pancreatic pain" – registry analysis

Study design, setting, and population

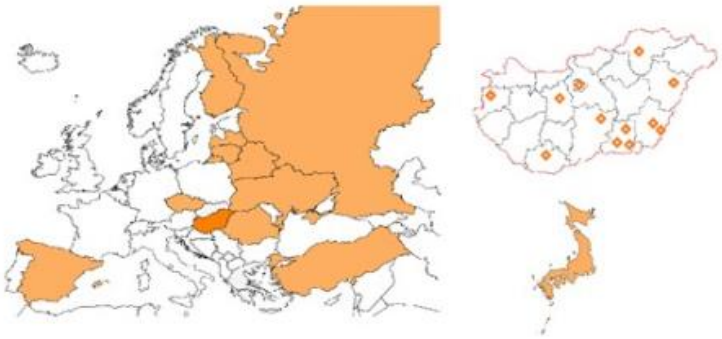

Figure 1. Centre Distribution

This study is a post-hoc cohort analysis of a prospective international registry conducted by the HPSG, which collected data on consecutive acute pancreatitis cases between 2012 and 2017. There was 1435 adult (≥18 years) patients enrolled from 19 Hungarian and eleven foreign institutions. Acute pancreatitis was diagnosed when two out of the three criteria were met (typical abdominal pain for acute pancreatitis, pancreas enzymes at least three times greater than the normal upper limit, and abnormal findings on abdominal imaging).

Pain assessment (groups): patients were classified into subgroups based on pain assessment. To our knowledge, there are no specific recommendations for pain assessment in acute pancreatitis; hence, we evaluated pain based on categories commonly used in clinical practice (Figure 2, Figure 3).

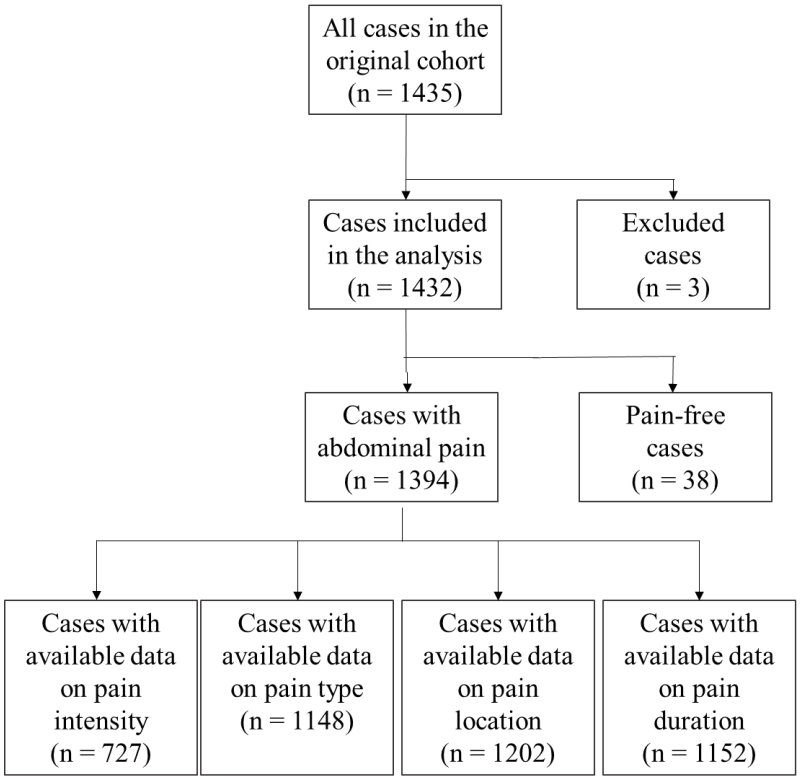

Figure 2. Flowchart of included cases

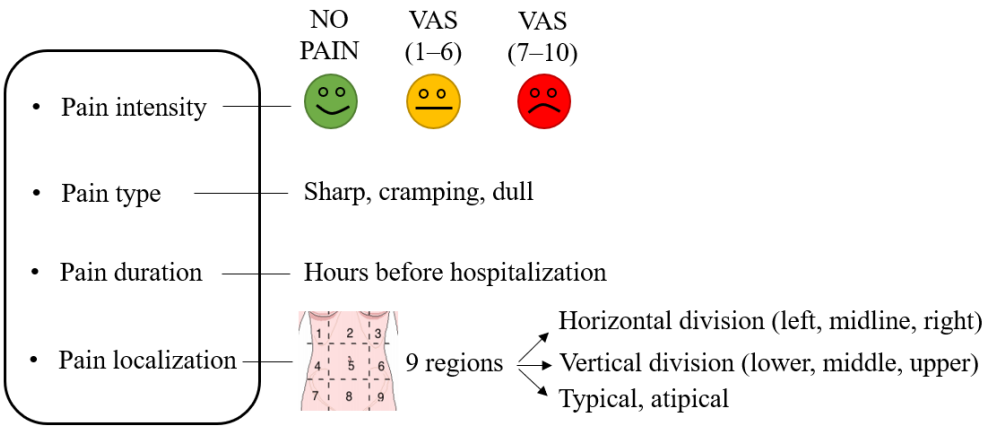

Figure 3. Pain characteristics groups (VAS; Visual Analog Scale)

Outcomes

*Primary outcome*s: the severity of AP and complications were defined based on the revised Atlanta classification. The revised classification differentiates between mild (no local or systemic complications), moderate (local complication or organ failure persisting no more than 48 hours), and severe AP (organ failure lasting more than 48 hours). We studied other outcome measures, such as hospital mortality, LOS, and new-onset diabetes.

Secondary outcomes: in-hospital opioid use was defined when there was evidence of opioid administration at least once during hospitalization. We also calculated the number of days with analgesics (NSAIDs, paracetamol, or opioids) if the details of pain management were available for the whole hospital stay. Where possible, the number of days with opioids was also calculated.

Statistical analyses: The analysis was performed with descriptive statistics, odds ratio (OR) with 95% CI (for dichotomous data in the main analysis), $\chi 2$ test with the Z test (for categorical data in the main analysis), the Mann–Whitney test, the Kruskal–Wallis test with the Mann–Whitney test as a post hoc test, and the Bonferroni correction to adjust Spearman's rank correlation (for continuous data in the main analysis). A two-sided p-value of <0.05 was considered statistically significant. The available-case analysis was used for missing data.

3.2. Methods – "Pain after bariatric surgery" – meta-analysis

We reported this systematic review and meta-analysis following the Preferred Reporting in Systematic Reviews and Meta-analyses (PRISMA) Statement. We included full-text RCTs that assessed the efficacy of perioperative USG-TAP block in postoperative analgesia compared with no treatment or sham intervention in patients who underwent laparoscopic bariatric surgery. The following outcomes were analyzed: pain scores measured by the VAS or the NRS on a scale from 0 to 10 within the first 24 postoperative hours, morphine requirement (mg) within the first 24 postoperative hours, time to ambulate (hours), length of hospital stay (hours). A systematic search was carried out in the following databases for studies published up to September 2019: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via PubMed), Web of Science, and Embase. We designed a search key with synonyms to bariatric surgery (population) and TAP (intervention) linked with Boolean operators. Two investigators independently removed did the selection, date extraction, and the risk of bias assessment with the revised Cochrane risk-of-bias 2 (RoB 2) tool. Disagreements were resolved by consensus.

Statistical analysis: we calculated mean differences with 95% CI between the control and USG-TAP groups. In the case of dichotomous data, we calculated risk ratio with 95% CI. A p value < 0.05 was considered statistically significant. Pooled estimates were calculated with a random effects model by using the DerSimonian-Laird method. Results of the meta-analysis were displayed graphically using forest plots. Heterogeneity was tested by using the Cochrane's Q and the I^2 statistics, a p value < 0.10 was considered statistically significant heterogeneity. All meta-analytical calculations were performed by Stata 11 data analysis and statistical software (Stata Corp LLC, College Station, TX, USA).

4. RESULTS

4.1. Results – "Acute pancreatic pain" – registry analysis

	Overall (n=1432)
Age, years, median (Ql-Q3)	57 (43-69)
Gender	
Male, n (%)	817 (56.9)
Female, n (%)	618 (43.1)
Medication taken regularly*	
NSAIDs or paracetamol	31 (2.9)
Opioid, n (%)	5 (0.5)
Benzodiazepines, n (%)	96 (9.0)
Antidepressants, n (%)	30 (2.8)
Anticonvulsant, n (%)	20 (1.9)
Etiology (pure)	
Biliary, n (%)	564 (39.4)
Alcoholic, n (%)	305 (21.3)
Hypertriglyceridemic	83 (5.8)
Post-ERCP, n (%)	41 (2.9)
Idiopathic, n (%)	300 (20.9)
Other, n (%)	139 (9.7)
Length of hospital stay, median (Ql-Q3)	9 (6-13)
Mortality, n (%)	36 (2.5)
Severity of pancreatitis	
Mild, n (%)	987 (68.9)
Moderate, n (%)	368 (25.7)
Severe, n (%)	77 (5.38)
Local complications, n (%)	435 (30.5)
Fluid collection, n (%)	373 (26.2)
Pseudocyst, n (%)	126 (8.8)
Necrosis, n (%)	132 (9.3)
Systemic complication, n (%)	115 (8.1)
Respiratory failure, n (%)	68 (4.8)
Heart failure, n (%)	26 (1.8)
Renal failure, n (%)	43 (3.0)

*data on medication taken regularly was available in 1069 cases

Table 1. General characteristics of the general population

Most of the patients described their pain as VAS 7–10 (n=511; 70.3%), characterized as cramping (n=705; 61.4%), localized in the upper abdomen (n=525; 46.4%), and starting within 24 hours prior to admission (n=682; 56.7%).

Pain intensity: it was not associated with age, gender, smoking habit, history of pancreatic diseases or metabolic diseases, Charlson Comorbidity Index (CCI), or findings on physical examination. Pain intensity as an ordinal variable was associated with the disease severity ($p<0.021$). Patients with VAS 7–10 pain on admission were more likely to require opioids during their hospital stay (OR=2.561, 95% CI: 1.573–4.169) than patients with VAS 1–6. Higher pain intensity on admission was also associated with the duration of the analgesic treatment (median two days IQR (1–5) in VAS 1–6 vs median three days IQR (2–5) in VAS 7–10, $p=0.009$), but not with the duration of opioid treatment.

Pain localization: an unexpectedly high percentage of patients (n=557, 50.8%) had atypical pain on admission, mainly with umbilical or right rib pain. In addition, we found a greater chance of atypical pain with obesity (OR=1.320 95% CI: 1.036–1.681), hypertension (OR=1.303 95% CI: 1.016–1.669), and hyperlipidemia (OR=1.889 95% CI: 1.302–2.741).

Pain duration: median pain duration on admission was 24 hours (IQR 10–72 hours). Pain duration on admission was not associated with age, gender, smoking habit, history of pancreatic diseases or metabolic diseases, CCI, or findings on physical examination. Surprisingly, pain duration prior to hospitalization was not associated with severity, mortality, LOS, or different systemic or local complications. While patients with pain duration of fewer than 24 hours prior to hospitalization required opioid administration more frequently compared to patients with longstanding pain (≥72 h) (22.9% vs 9.2%, $p<0.001$).

Pain type: comparing patients with different types of pain, we found no difference in age, gender, BMI, history of pancreatic diseases, DM or other metabolic diseases, or findings on the physical examination. Patients with cramping pain tended to have a biliary etiology, and they were less likely to have an alcoholic etiology compared to dull or sharp pain ($p<0.05$)

Sharp pain was associated with a 2.6-fold increase in mortality odds (OR=2.632, 95% CI 1.063–6.514) compared to other types of pain (dull + cramping pain). Sharp pain might also be a risk factor for severe disease (OR=2.206, 95% CI: 1.199–4.059), especially for systemic complications (OR=2.481, 95% CI: 1.550–3.969), including new-onset diabetes (OR=2.561, 95% CI: 1.472–4.456) and respiratory (OR=3.220, 95% CI: 1.806–5.740) and heart failure

(OR=3.222, 95% CI: 1.319–7.869). There were also increased odds for necrosis development with sharp pain (OR=1.653, 95% CI: 1.060–2.580). Cramping pain was associated with a longer LOS ($p<0.05$) (Figure 5 and Table 4).

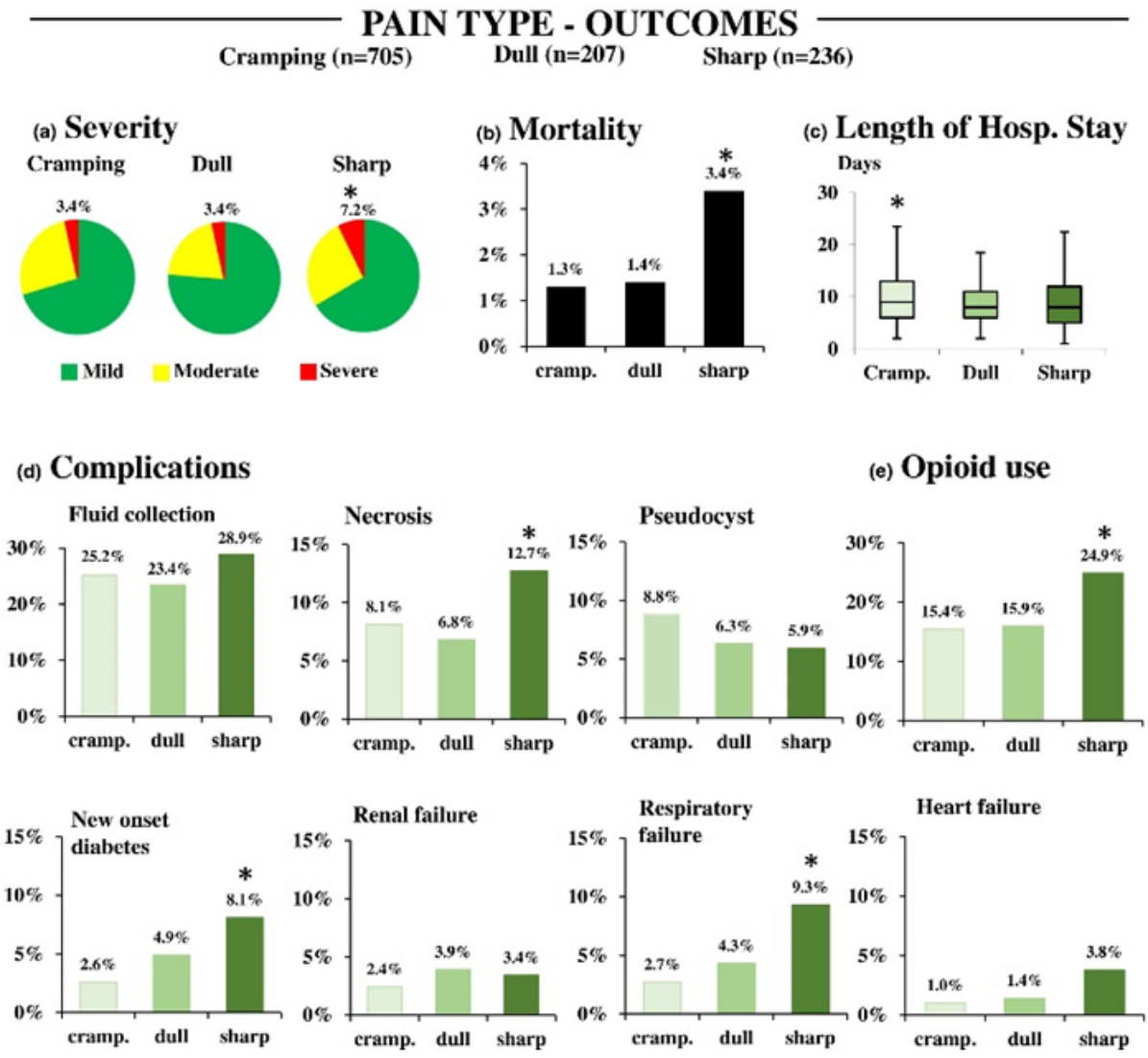

Figure 5. Main outcomes of AP in pain type groups (cramping and dull vs. sharp). (a) Severity (*OR = 2.206 95%: 1.199–4.059); (b) Mortality (*OR = 2.632 95% CI: 1.063–6.514) Length of hospital stay (*p < 0.05); (d) Complications: fluid collection; necrosis (*OR = 1.653 95% CI: 1.060–2.580); pseudocysts; new-onset diabetes (*OR = 2.561 95% CI: 1.472–4.456); respiratory failure (OR = 3.220 95% CI: 1.806–5.740); renal failure; heart failure (*OR = 3.222 95% CI: 1.329–7.869); (e) Opioid use (*OR = 3.250 95% CI: 1.585–3.194)

Pain management: 745/882 (85.5%) patients were administered analgesics at least once during the hospital stay, out of whom 678/882 (76.6%) received them on the day of admission. Opioids were administered at least once during the hospital stay in 155 cases (17.6%). The median duration of pain management was three days (IQR 2–6). In the patient group requiring

analgesics, the median LOS was eight days (IQR 6–12) compared to patients without pain management, where LOS was seven days (IQR 5–11) (p<0.001). The median length of opioid therapy was two days (IQR 1–4). In the patient group requiring opioids, the median LOS was nine days (IQR 5–14) compared to patients without opioid therapy, where LOS was eight days (IQR 6–13) (p<0.001).

4.2. Results – "Pain after bariatric surgery" meta-analysis

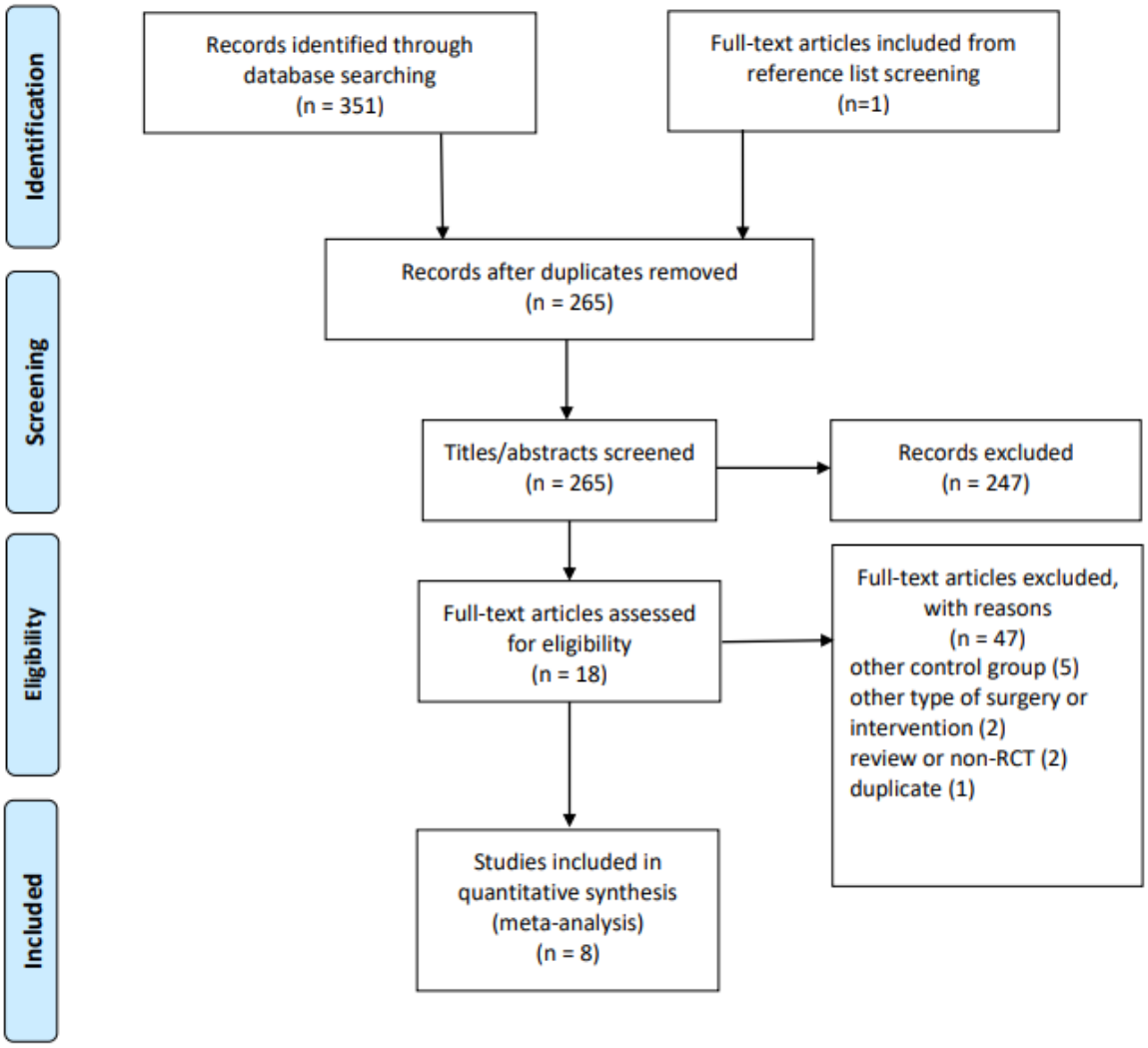

Figure 6. Flow chart of study selection and inclusion process

Pain Scores Within the First 48 h: Pooled analysis showed that USG-TAP block lowered postoperative pain scores (rated on a scale between 0 and 10) at rest by 2.25 ($p < 0.001$) at 1 h, by 1.08 ($p < 0.001$) at 3 h, by 2.25 ($p < 0.001$) at 6 h, by 1.23 ($p < 0.022$) at 12 h, and by 0.83 ($p = 0.006$) at 24 h (Fig. 6a). Heterogeneity was considerable in these analyses (Figure 6a).

Postoperative Cumulative Morphine Dose: we identified significantly lower opioid requirement in the USG-TAP block (Figure 6b).

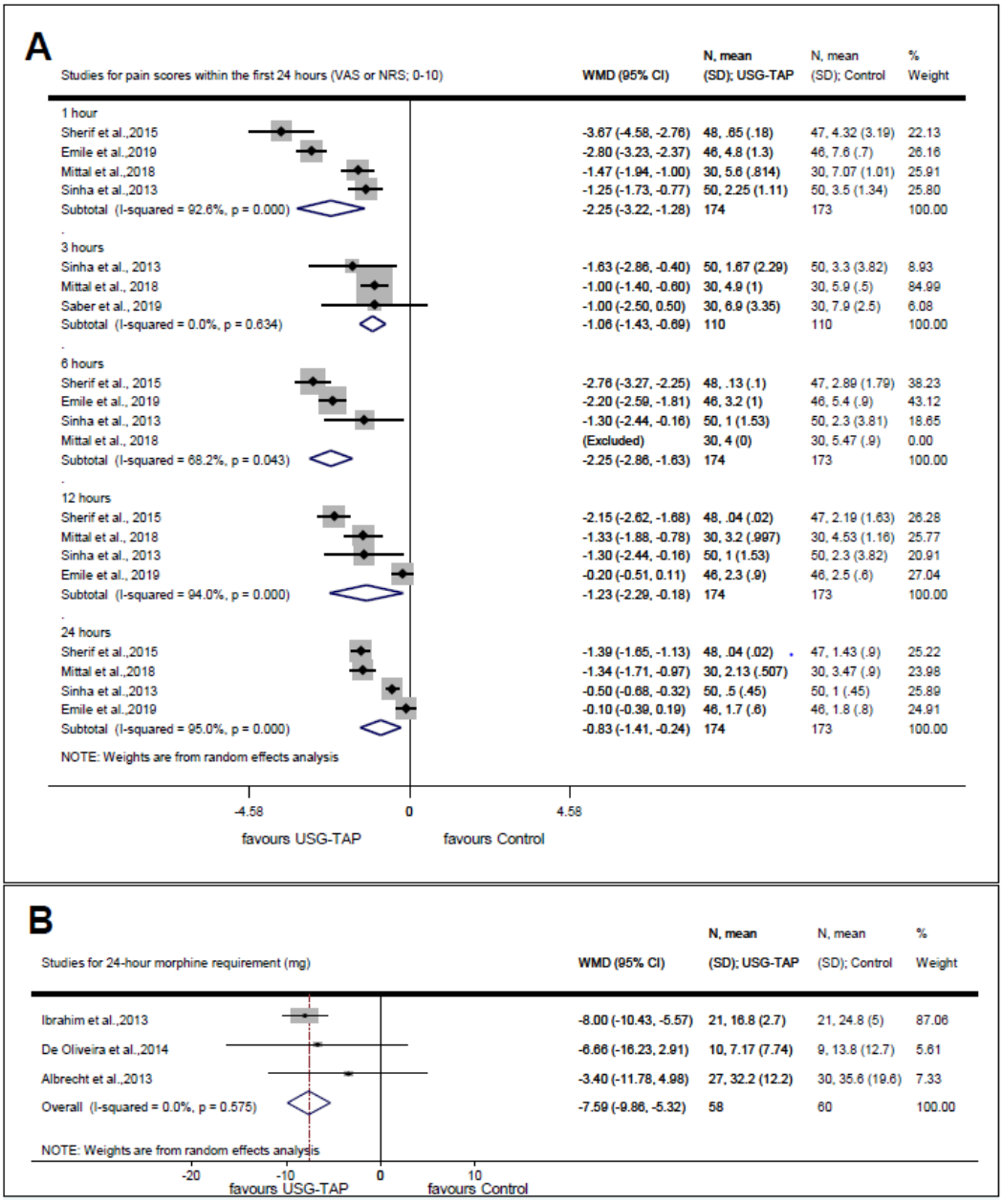

Figure 6. Forest plots that show efficacy endpoints for the comparison of ""USG-TAP"" and ""control"". A) Forest plot for pain score within the first 24 postoperative hours (VAS or NRS, 0–10). B) Forest plot showing 24-h postoperative morphine requirement (mg). VAS, Visual Analog Scale; NRS, Numbering Rating Scale

Time to Ambulate: Pooled analysis of four trials with 347 patients (174 in the intervention group and 173 in the control group) demonstrated that the time to ambulate was shorter by 2.2 h in patients who underwent USG-TAP block ($p = 0.009$).

Length of Hospital Stay: A meta-analysis of three studies with 168 patients (83 in the intervention group and 85 in the control group) failed to identify a shorter length of hospital stay following USG-TAP block performance compared with that of controls ($p = 0.102$).

5. DISCUSSION

In these two analyses, we explored new aspects of pain assessment and management. We expect our results to be integrated into personalized medicine.

Interestingly, in our *registry analysis*, we discovered an unexpected feature of sharp pain: it was associated with unfavorable disease outcomes, such as higher systemic complications and mortality rates. Previous data suggest that pain type (quality descriptors) might be related to the pain mechanism. Understanding this pain mechanism can aid in choosing the optimal therapeutic approach.

While we might think that, as in other acute illnesses, prolonged pain prior to hospitalization results in a worse prognosis, this does not seem to be the case. An explanation for this controversy may be that patients with more intense and sharp abdominal pain turned to doctors earlier in our study.

We could not confirm gender or age-dependent pain pattern in the cohort analysis. Moreover, patients requiring more pain medication on admission could also expect a more prolonged need for pain management.

We briefly reviewed the use of opioid and non-opioid pain medications in our registry. Opioids were given relatively infrequently considering the very strong pain in AP. Despite the steady rise in opioid consumption, Central and Eastern Europe, from where our data originate, has a more restrictive opioid policy.

Our *meta-analysis* also points to the advantages of multimodal analgesia. TAP block, a local anesthetic technique as part of appropriate multimodal analgesia can significantly improve postoperative pain compared to treatment without TAP block. Besides, it can accelerate patient recovery. It reduces the side effects of opioids, since patients who received TAP block required

significantly fewer opioids. Our meta-analysis also indicated a shorter time required to ambulate with USG-TAP block.

In our *registry analysis*, cases administered with painkillers, especially with opioids had longer LOS compared to patients without a painkiller and opioids, respectively. Although this might seemingly contradict the pre-assumption that adequate analgesia reduces hospital stay, patients in the cohort were not treated with rigorous, predetermined pain management strategies but instead based on physicians' preferences.

Although there is still no specific therapy in AP, pancreas research decreased between 1965 and 2015. Therefore; it is crucial to make efforts in the translation of research to organize specific care for pancreatic diseases, to use existing knowledge, to identify further research needs and to communicate the results to community benefit. We would highlight the importance of guideline development. Guidelines similar to ERAS might also be advantageous in AP, including proper pain management, nutritional guidance, and physiotherapy. To fully elucidate the content of an enhanced recovery guideline in AP, we need to know more about the characteristics and pathomechanism of AP. This concept may accelerate healing and reduce the length of hospitalization, protecting patients from the possible complications of long hospitalization and incorrect or excessive therapy and preventing the recurrence of AP.

Strength & limitations

The *registry analysis* examines the role of abdominal pain in AP in a unique and detailed fashion. The data came from an international, multicenter collaboration with 1432 consecutive patients with AP, thus improving its external validity.

This study also has limitations. First, a high percentage of missing data in some variables can lead to selection bias. Second, we collected data on pain at a single point in time on the day of hospital admission. Third, a registry analysis is not suitable to draw a conclusion on the efficacy and safety of therapies.

Concerning the *meta-analysis*, heterogeneity was high between studies included. Since the low number of analyzed studies did not allow subgroup analyses, we could not explore the cause of heterogeneity. Theoretically, we can explain heterogeneity by the different types of surgery, anesthetic management, dose and type of anesthetics, USG-TAP approach, or postoperative analgesia regimen.

Further limitation can be that some studies were conducted before the "paradigm shift" in opioid use, which means that these studies might apply non-opioids inadequately.

6. CONCLUSION

Implication for practice

According to our registry analysis, an intense and sharp pain on admission was associated with higher odds for severe AP and several systemic and local complications. Therefore, a comprehensive patient interview should include questions about pain characteristics, and patients with intense and sharp pain might need closer monitoring.

According to our meta-analysis, our results support the incorporation of USG-TAP block into multimodal analgesia regimens of ERAS protocols for bariatric surgery, which has happened in the 2021 update.[93]

The development of enhanced recovery guidelines in AP might be worth considering.

Implications for research

Acute abdominal pain is the leading presenting symptom in acute pancreatitis; however, we currently lack specific guidelines for pain assessment and management. We also need to know more about the pathophysiology of pain type to improve personalized medicine.

7. SUMMARY OF NEW RESULTS

"Acute pancreatic pain" – registry analysis

It is the most thorough study that investigates the role of pain in acute pancreatitis, with the highest case number. Its novelty lies in the fact that it examines pain as a complex phenomenon.

1. Acute pancreatic pain was mostly severe, cramping, epigastric or upper abdominal belt-like that begins within 24 hours prior to hospitalization.
2. Characteristics of pain were not influenced by gender or age.
3. The more intense and sharp pain was associated with worse disease outcome
4. Opioid administration was relatively infrequent compared to the high proportion of patients with very intense pain.

7.2. "Pain after bariatric surgery" – meta-analysis

TAP block was associated with lower postoperative pain score and 24-hour cumulative morphine dose, also with shorter time to ambulate. Thus, TAP block could be recommended as an efficient part of multimodal analgesia in the 2021 update of ERAS society guidelines.

9. ACKNOWLEDGEMENT

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