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The Efficacy and Safety of Using Opioids in Acute Pancreatitis: an Update on Systematic Review and Meta-Analysis

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ABSTRACT

Background: Most patients with acute pancreatitis (AP) suffer from abdominal pain that requires immediate pain relief, and there are various medication choices available, with opioids being the most prescribed analgesics. **Objective:** Our objective is to compare the use of opioids with other medications in emergency settings for managing pain in patients with AP. **Methods:** A systemic search was conducted in electronic databases (PubMed/Medline, Cochrane Library, Embase and Google Scholar) from inception to Feb 2023. All statistical analyses were conducted in Review Manager 5.4.1. The study's inclusion criteria was then selected. Only those Randomized Controlled Trials were involved that included patients having AP in an emergency setting. A random-effect model was used when heterogeneity was seen to pool the studies, and the result was reported in the Odds Ratio (OR) and Mean Difference (MD) along with the corresponding 95% confidence interval (CI). Narrative analysis was conducted for those variables which did not have sufficient data be included in the quantitative analysis. **Results:** We include eight Randomized Controlled Trials in our study. The Pooled result showed non-significant differences in adverse effects between the two interventions (OR 1.42 [95% CI 0.62, 3.23]; p value= 0.40; I2= 20%). While overall, significantly additional drugs were used in the control group (OR 0.22 [95% CI 0.06, 0.85]; p value= 0.03; I2= 72%). Pain score and severity levels were also analyzed. We used a narrative approach to analyze the length of stay, mean time to reach significant decrease in pain, and mortality, which were all non-conclusive. We also narratively assessed the Pediatric population. **Conclusion:** Opioids do not provide significant superiority over other medications and should be avoided due to their addictive nature.

Keywords: Acute Pancreatitis, Emergency, Opioids.

1. BACKGROUND

The Acute pancreatitis (AP) is an inflammatory disease of the pancreas with the elevation of pancreatic enzymes that develops suddenly and goes away in a few days to weeks. Approximately 2,814,972.3 (95% UI 2,414,361.3–3,293,591.8) cases were reported globally with 115,053.2 (104,304.4–128,173.4) deaths in 2019 (1). Risk factors for AP include gallstones, alcohol use, surgical trauma, hypercalcemia, hypertriglyceridemia, infection, and autoimmune diseases (2). AP is most commonly associated with gallstones and chronic alcohol abuse. Abdominal pain localized to the epigastric region or left upper region is the cardinal symptom of AP (3). The pain is severe in intensity and tends to last for a few days. It is diagnosed based on clinical evaluation, laboratory tests (serum amylase, lipase, and calcium), and investigations (contrast-enhanced CT and transabdominal ultrasound) (4). Initial management of AP includes intravenous fluid resuscitation, adequate analgesia using either NSAIDs or opioids, and nutritional support (4).

The mechanism by which NSAIDs control pain is through inhibiting cyclooxygenase-dependent prostaglandin formation (5). Drugs like diclofenac, ketorolac, dexketoprofen, and metamizole have been used for managing pain in AP. A systematic review was carried out to assess the role of NSAIDs in acute pain management in AP. The results showed that they were effective in relieving pain and in improving systematic complications (6). Pezzilli et al.

also concluded in their systematic review that NSAIDs are able to manage acute pain in AP (7).

Opioids are also commonly used for treating acute pain and they work by inhibiting neurotransmitter release in presynaptic terminals; thus, preventing the conduction of pain signals in the spinal cord (8). Opioid works on various receptors found centrally and peripherally. Mu receptors are located in the brainstem and thalamus with subtypes Mu1 and Mu2 (8). Mu1 receptors are mainly responsible for supraspinal analgesia and causing euphoria. Mu2 receptors are responsible for respiratory depression, dependence, and sedation. Kappa (κ) receptors are found in the prefrontal cortex, limbic system, and spinal cord (8). They are responsible for spinal analgesia, sedation, stress, and dependence. Delta (δ) receptors are located in the brain, spinal cord, and dorsal root ganglion (8). These receptors mainly act by reducing persistent pain.

Opioids are classified as agonists (morphine and fentanyl), partial agonists (e.g., buprenorphine), agonist-antagonist (e.g., pentazocine), and antagonists (e.g., naloxone) (8, 9). Morphine is a long-acting opioid (9). It is a strong Mu agonist and a weak κ-receptor agonist. Side effects include orthostatic hypotension and respiratory depression by acting on the nucleus accumbens and releasing histamine. Morphine can cause spasms of the sphincter of Oddi and urinary bladder trigone, thereby resulting in urinary retention. Fentanyl is also a strong opioid agonist working mostly on Mu receptors and is available in transdermal and parenteral preparations (9). Buprenorphine is a partial agonist that acts on the Mu receptor (10). Its side effects are sedation, dizziness, headache, and respiratory depression which can be reversed by naloxone. Opioids like pentazocine are categorized as agonist-antagonists because of poor Mu receptor efficacy and partial κ-receptor agonistic action (10). Naloxone is an opioid receptor-antagonists naloxone that competitively antagonizes the Mu, κ, and δ receptors (10).

It is used in the emergency department for the rapid reversal of opioid overdose. Common opioids used in the pediatric population are morphine, fentanyl, hydromorphone, meperidine, and methadone (11). Common adverse effects experienced by this group include constipation (50–65%), nausea (25–50%), sedation (20–60%), pruritus, and fatigue. Respiratory depression is a common cause of death due to opioid overdose (11).

A meta-analysis published in 2021 assessed the role of analgesics including opioids and NSAIDs in AP, and the need for rescue analgesia beyond the one being tested (12). Compared to the placebo, the tested analgesics greatly reduced the need for rescue analgesia and no significant difference was observed between opioids and nonopioids regarding the primary outcome for the need for additional pain relief (12). Thavanesan et al. conducted a meta-analysis comparing seven different analgesics in improving pain scores in patients of AP as reported by the visual analogue scale (VAS) (13). Improvement in VAS scores were comparable between opiates to non-opiates within 24 hours with no significant difference (P = 0.462) (13). Nelson et al. conducted a similar meta-analysis comparing opiates to non-opiates in AP patients (14).

Similar results were observed as there was no significant difference in pain severity after 24 hours (14). The risk of complications of pancreatitis like nausea, sedation, and death were comparable in both groups. The non-opiates group required additional analgesia more often than opiates (14).

2. OBJECTIVE

In our meta-analysis, we aim to overcome the gaps in the literature by including more recent Randomized Controlled Trials and pediatric populations, as previous systematic reviews and meta-analyses didn't include pediatric populations. The primary outcomes of this meta-analysis are the need for rescue analgesia and VAS within 24 hours. The rate of adverse events, mortality, and length of hospital stay are secondary outcomes.

3. MATERIAL AND METHODS

3.1. Search strategy and registration

Preferred Reporting Items for Systematic Review and Meta analyses (PRISMA) guidelines (12) were used to conduct this manuscript. Pubmed/Medline, Cochrane, Embase, and Google Scholar were used to conduct the literature search from inception to Feb 2023. Each database was scoured using search terms for "acute pancreatitis", "Adult or Pediatric" combined with multiple synonymous terms for "Analgesia" using the Boolean operator "AND"/ "OR".

We manually screened the related articles and their references. We will include clinicaltrials.gov (1964 to present) to search for trials. Protocol was registered in PROSPERO with following number: CRD42023384797.

3.2. Eligibility criteria

The articles following PICOS were eligible: P (Population): People with AP; any age, any gender and Population not restricted to Saudi Arabia; will examine papers from all over the world; I (Intervention): Opioids; (Control): All pain management agents without limitations, we will even include traditional medicine such as Electroacupuncture; S (Studies): Randomized Controlled Trials, Cohort, and Cross-sectional studies.

3.3. Data extraction

We used MS Word to extract data and Zotero for referencing. Reviewers were asked to review independently one-by-one and Reviewer 3 will act as a moderator in case of disparity between the first two reviewers.

3.4. Quality Assessment

Two investigators will conduct quality assessment independently and any disagreement will be moderated by a third investigator or a senior author. The Cochrane Collaboration's tool will be used to assess the risk of bias for Randomized Controlled Trials. For each component of the tool, low, high, or unclear risk of bias levels will be used for judgement, and the summary will be presented in the form of a table (Table 1). New Ottawa scale will be used to assess cohort studies and cross-sectional studies

Study	Adequate Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Free of Other Bias	Net Risk of Bias
Ebbehøj et al. 1985	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Moderate Risk
***Jakob et al*. 2000**	Low Risk	Low Risk	Unclear Risk	Low risk	Low Risk	Low Risk	Low Risk	Low Risk
Stevens *et al.* 2002	Unclear Risk	Low Risk	High Risk	Unclear Risk	Low Risk	Low Risk	Unclear Risk	Moderate Risk
Kahl *et al*. 2004	Low Risk	Unclear Risk	High Risk	Low Risk	Low Risk	Low Risk	Unclear risk	Low Risk
Peiro *et al*. 2008	Low Risk	Low Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Wilms et al. 2010	Unclear Risk	Unclear Risk	Low Risk	Unclear Risk	Low Risk	Unclear Risk	Unclear Risk	Moderate Risk
Layer et al. 2011	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Sadowski et al. 2015	Unclear Risk	Unclear Risk	Unclear Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Gulen *et al*. 2016	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Mahapatra *et al*. 2019	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low risk	Low Risk
Dong *et al*. 2019	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Kumar *et al*.2020	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Table 1. Quality assessment of the Randomized controlled trials

Studies	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts	Total Score
Grover et al. 2018	1	1	1	1	2	1	1	1	9
Földi et al. 2022	1	1	1	1	2	1	1	1	9

Table 2. Quality assessment of cohort studies

Studies	Selection (Maximum 5)				Comparability (Maximum 2)	Outcome (Maximum 3)		Total score
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of the outcome	Statistical test	
Perito et al. 2020	1	1	1	2	2	1	1	9

Table 3. Quality assessment of cross-sectional studies

(Table 2 and 3). A score <6 is high risk, 6–7 is moderate risk and >7 is low risk.

3.5. Data Synthesis:

Data will be extracted using MS Excel sheet (mean, standard deviations, and end point events). Missing data will be managed according to protocols and any other method made suitable by the authors. Review Manager v5.3.5 will be used to conduct quantitative analysis using random-effects model. Continuous data will be pooled as Mean Difference (MD) and its 95% confidence interval (CI) and dichotomous data will use Odds Ratio (OR) and its 95% CI. Heterogeneity will be evaluated using I2 (I2 ≥ 50% or p < 0.1 indicative of high heterogeneity). Moreover, P< 0.05 will be considered statistically significant. While Narrative analysis will be conducted for data variables and factors which are not deemed suitable enough to carry out quantitative analysis, Subgroup analysis will also be undertaken if needed.

4. RESULTS

4.1. Literature search

Our initial literature search provided 1011 articles. Further, 702 articles remained after removing the duplicates and finally, 70 articles were left for full-text review. Additionally, 15 studies were finalized to conduct this Systematic review and meta-analysis.

4.2. Baseline characteristics

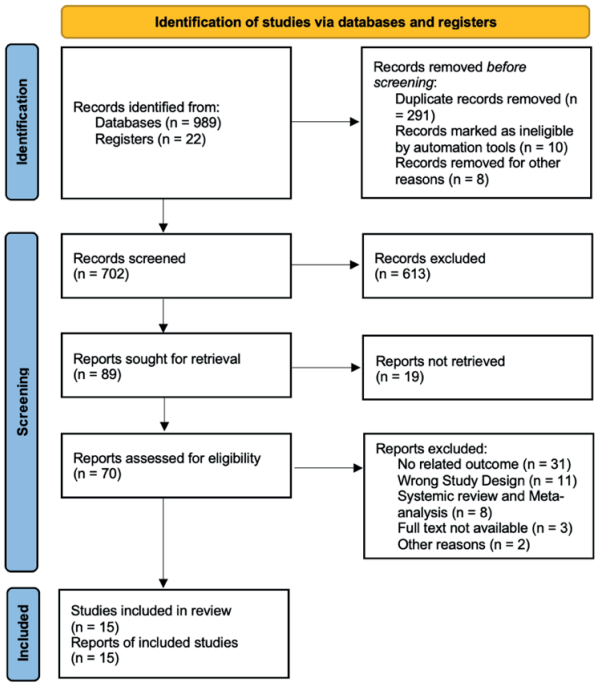

Figure 1 shows the Prisma flow chart.

Table 4 shows basic characteristics of the studies used in our manuscript (16–30). Out of the total studies, 12 were Randomized Clinical Trials, two studies were retrospective cohorts, and one was a cross-sectional study. We had five studies from USA, four studies from Germany and one of each from Denmark, India, Hungary, Switzerland, Spain, and Turkey. We included 2637 patients. The mean age was 54.38 years.

4.3. Publication Bias and Quality assessment

Less than 10 articles were included in the meta-analysis, so publication bias was not assessed. All studies had a low risk of bias except Stevens et al. and Wilms et al. which had a moderate risk of bias (Tables 1–3).

4.4. Result of Quantitative analysis

Seven studies were included in quantitative analysis (16–22). Quantitatively, we analyzed three factors: Adverse effects, Use of additional drugs, and Pain score.

4.4.1 Adverse effects

Five studies were utilized to analyze adverse effects (17, 19–22). In these, 164 patients were present in the Opioids group, while 169 patients were present in the control group. Pooled result (Figure 2) showed that there was no significant difference in adverse effects between the two interventions (OR 1.42 [95% CI 0.62, 3.23]; p value= 0.40; I2= 20%).

4.4.2 Use of Additional Drugs

Five studies with two subgroups (Add-on and Rescue drugs) were used to analyze the usage of additional drugs between the two groups (16-18, 21, 22). Three studies were present in the Add-on subgroup and two studies

Study	Year	Study design	Duration	Country	BMI (kg/m²)	Total Patients (n)	Male (%)	Mean Age (years)	Population	Opioid used	Qualitative or Quantitative	Risk of Bias
Ebbehøj et al.	1985	RCT	N/A*	Denmark	N/A*	30	66.6	N/A*	Adult	N/A*	Qualitative	Low Risk
Jakobs et al.	2000	RCT	N/A*	Germany	N/A*	40	57.5	49.5	Adult	Buprenorphine	Both	Low Risk
Stevens et al.	2002	RCT	N/A*	USA	N/A*	32	56.2	N/A*	Adult	Fentanyl and Demerol	Qualitative	Low Risk
Kahl et al.	2004	RCT	N/A*	Germany	N/A*	101	71.2	45	Adult	Pentacozine	Both	Low Risk
Peiró et al.	2008	RCT	N/A*	Spain	N/A*	16	50	54.7	Adult	Morphine and Pethidine	Both	Low Risk
Wilms et al.	2010	RCT	April 2003-July 2005	Germany	26	42	52.3	54.2	Adult	Buprenorphine	Qualitative	Moderate Risk
Layer et al.	2011	RCT	Dec 2003-July 2005	Germany	N/A*	44	59	N/A*	Adult	Buprenorphine	Qualitative	Low Risk
Sadowski et al.	2015	RCT	July 2005-Aug 2010	Switzerland	28.4	35	55.1	60.2	Adult	Fentanyl	Qualitative	Low Risk
Gülen et al.	2016	RCT	Jan-June 2014	Turkey	N/A*	90	58.9	53.5	Adult	Tramadol	Both	Low Risk
Grover et al.	2018	Retrospective study	Jan 2013-Dec 2015	USA	N/A*	211	36	N/A*	Pediatric	Morphine, hydromorphone, fentanyl, oxycodone, tramadol	Qualitative	Low Risk
Mahapatra et al.	2019	RCT	May 2016-May 2017	USA	N/A*	50	48	38.2	Adult	Pentacozine and Fentanyl	Both	Low Risk
Dong et al.	2019	RCT	July 2016- April 2017	USA	N/A*	46	45.7	53.1	Adult	Hydromorphone and Morphine	Both	Low Risk
Kumar et al.	2020	RCT	July 2015-Nov 2016	India	N/A*	41	65.8	47.3	Adult	Tramadol	Both	Low Risk
Perito et al.	2020	Cross-sectional study	Sep 2012-Aug 2017	USA	N/A*	427	42.5	12.5	Pediatric	Morphine, hydromorphone, fentanyl, oxycodone, tramadol, butorphanol, codeine, meperidine, methadone	Qualitative	Low Risk
Földi et al.	2022	Cohort	2012-2017	Hungary	N/A*	1432	56.9	N/A*	Pediatric	N/A*	Qualitative	Low Risk

Table 4. Baseline Characteristics of the studies . N/A*=Not available

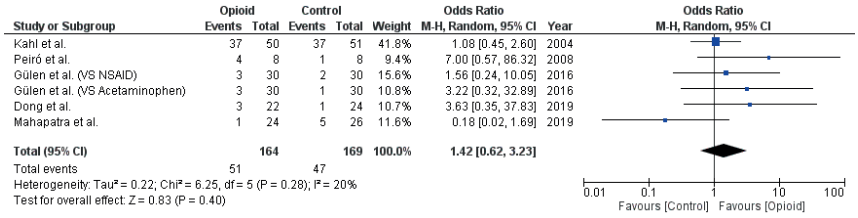

Figure 2. Forest plot showing the effect size of Adverse effects between Opioid and Control Groups

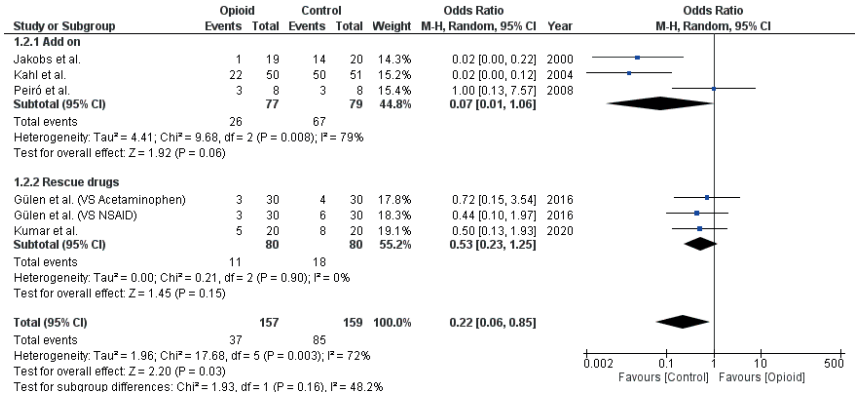

Figure 3. Forest plot showing effect size of Use of additional drugs between Opioid and Control Groups

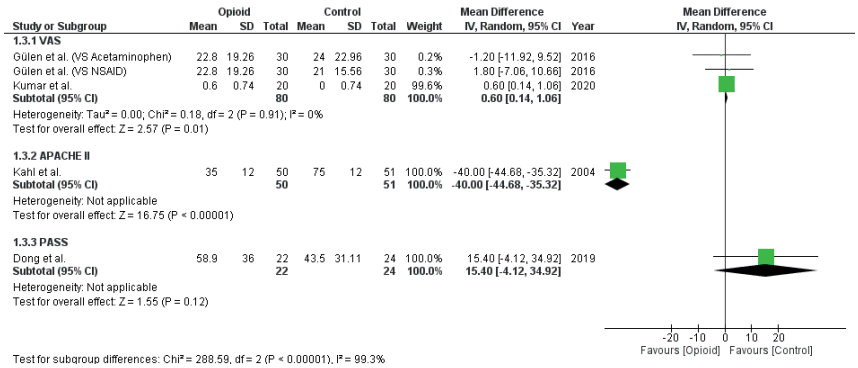

Figure 4. Forest plot showing effect size of Pain score and severity between Opioid and Control Groups

were present in the rescue drugs subgroup. Pooled result (Figure 3) showed that there was a non-statistical difference between the two groups; in Add-on (OR 0.07 [95% CI 0.01, 1.06]; p value= 0.06; I2= 79%) group and rescue drugs (OR 0.53 [95% CI 0.23, 1.25]; p value= 0.15; I2= 0%) group. Although, overall, it was seen that there was significantly more use of additional drugs in control group than opioids (OR 0.22 [95% CI 0.06, 0.85]; p value= 0.03; I2= 72%).

4.4.3. Pain Score and Severity Levels

Four studies were used based on three scales (VAS, APACHE II, and PASS) to analyze pain scores and severity levels (17,18,20,22). The pooled analysis (Figure 4) showed that there was statistically less pain in patients with opioid, according to VAS (MD 0.60 [95% CI 0.14, 1.06]; p value= 0.01; I2= 0%). Disease severity was assessed using APACHE II and PASS. APACHE II showed that opioid use resulted in better outcomes (MD -40.00 [95% CI -44.68, -35.32]; p value< 0.00001; I2= Not applicable). While PASS did not favor any group (MD 15.40 [95% CI -4.12, 34.92]; p value= 0.12; I2= Not applicable), due to a low number of studies, we can't completely comment on whether or not any intervention method is superior to the other.

4.5. Result of Qualitative analysis in adult population

Ten studies were included in qualitative analysis (16, 18-21, 23-27). We assessed three variables qualitatively: length of stay, mean time to reach significant decrease in pain, and mortality.

4.5.1. Length of Stay

Five studies provided data for length of stay (16, 18-20, 24). All the studies showed that there was statistically no difference in length of stay between the opioid group and control group. Dong et al. showed that both groups had a median stay of three days while Mahapatra et al. had median stay of four days (19, 20). Jakobs et al. showed a p value of 0.24 and Stevens et al. showed a p value of 0.41, owing to a statically non-significant result (16,18). Sadowski et al also showed a non-significant relation (p = 0.65) (24).

4.5.2. Mean Time to Reach Significant Decrease in Pain

Five studies recorded the mean time to reach a significant decrease in pain when the two interventions were given (18, 21, 25-27). There was a non-decisive result, in which Kumar et al. favored that control decreased the time significantly (p value 0.028) and Peiró et al. showed a non-significant difference (p value 0.169). Ebbehoj et al showed that opioids with Indomethacin had better outcomes. Wilms et al and Layer et al both showed that statistically positive results were observed. No strong results were postulated in the favor of opioids or control.

4.5.3. Mortality rate

Mortality was assessed by three studies (16, 19, 24). All studies showed that both groups didn't have any significant mortality associated with them. Jakobs et al. showed p value of 0.52, while in Mahapatra et al., only one patient died in the control group. Sadowski et al had no mortality reported (24).

4.6. Result of Qualitative analysis for Pediatrics population

Three studies were used to assess pediatrics population (28-30). Grover et al. showed that the use of opioids was much superior to non-opioid infusion. Shorter time was required while dosing in opioids group (p=0.001). Although, a higher initial dose was given in opioid group (p=0.01) (28). Perito et al. reported that frequent opioid use resulted in increased hospital admission (p<0.0002)

and emergency room (p<0.0002) visits and an increase in missed school days (p<0.0002) (29). Földi et al. discussed the characteristics of pain in AP which were presented in the emergency room. It showed that sharp pain was more associated with mortality (OR=2.263 [95% CI:1.199-4.059]). Moreover, atypical pain was observed in more than 50% of the population (30).

5. DISCUSSION

In this systematic review and meta-analysis, we present the assessment of evidence from 15 studies to evaluate the role of opioids as an analgesic in the management of AP. The qualitative and quantitative results suggested no significant and superior role of in opioids in comparison to the control group in both adult and pediatric population. Metamizole, NSAIDs, and local anesthetics were compared with opioids; however, no significance of opioids over the other therapies could be established in terms of adverse effects, pain severity, use of an additional drug, length of hospital stay, and mortality. The major adverse effects associated with opioids were nausea, vomiting, and a short episode of hypotension. In pediatric population, only one study favored the use of opioids over non-opioids control, while reporting a shorter time to reach significant decrease in pain and superior analgesic effect. However, the results were inconclusive due to the lack of sufficient data availability on the subject, Peiro et al. conducted a pilot study to compare morphine with metamizole. They reported no significant association between morphine in pain relief and metamizole (21). Gulen et al. compared the synthetic opioid tramadol with paracetamol and dexketoprofen in adult AP patients; there was no difference among the three groups. Nausea and hypotension were reported in two patients in comparison to nausea and vomiting in three patients in the control group (22).

Kumar et al. found diclofenac and tramadol equally effective in controlling pain AP. Both drugs were also similar in the requirement of additional analgesia and the number of painful days (18). Another trial that compares diclofenac with pentazocine, showed results favoring opioid agonists for pain relief, a lesser dose of additional analgesia, and a longer pain-free time. There was no difference in the adverse effects of the drugs (19).

The results published by Jakobs et al. favored opioid use. They compared buprenorphine with procaine. The authors reported significantly less requirement for additional analgesia with buprenorphine and a significantly low pain score. However, buprenorphine was associated with higher adverse effects, predominantly nausea and vomiting. The sedation rate of buprenorphine was higher than procaine (16). Kahl et al. also compare procaine with an opioid, pentazocine (17). They showed similar results to Jakobs et al. in terms of additional analgesics and pain relief (16, 17). A statistically non-significant difference in adverse effects was reported in both groups, and altered bowel function was the major adverse effect. However, the result by Dong et al. favored the use of non-opioid treatment. They found significantly improved refeeding time associated with non-opioids therapy in comparison to opioids (20). Ebbehoj et al. reported data of 30 patients with AP on indomethacin and opioids in comparison to the placebo. They found indomethacin remarkably effective in pain relief in AP; however, their trials were too small to for concluding results regarding the prognostic values of opioids (25). Layer et al. also present an inconclusive result regarding the use of opioids. However, they reported significant improvement in pain, and less readmission rate in comparison to the placebo. The biological properties of opioids exerting in vitro and in vivo effects result in potent anti-inflammatory effect, without impairing the host defenses and modulating the gastrointestinal motor function (27). Grover et al. published the first study reporting initial pain management in AP patients in pediatric population. Despite the development of new drugs and techniques, it is difficult to manage peri-operative pain in children; therefore, the opioids remain the gold standard practice. Grover et al. showed opioids as superior to placebo in terms of pain management. However, they reported that despite the superior effect of one analgesic over the other in emergency settings, the decision for choosing the analgesic is more subjective than objective (28). Similar results regarding pain interference with the use of opioids were reported by Perito et al. in another pediatric study (29). Basurto et al., in 2013, published a meta-analysis to compare the role of opioids in AP in comparison to non-opioids; they pooled the data from four RCTs and they found no significant role of opioids over non-opioids available (31). Later in 2021, Cai et al. updated the result with the addition of three more RCTs; they found opioids superior to non-opioid analgesics, mainly procaine (12). Unlike the results published by Cai et al., our pooled results drew a result showing no significance of opioids over other analgesics for AP.

The spasm of sphincter of Oddi was observed with morphine use, limiting the morphine prescription in AP (32). However, due to a lack of literature on this subject, the use of opioids is still contraindicated (21,33). Despite the debate, NSAIDs and opioids are considered as first-line treatment options in AP (34,35). Another concern for opioid use is potential respiratory depression and paralytic ileus at higher doses (36); however, none of the included studies reported these symptoms. The misuse and abuse of opioids following chronic use is a potential adverse effect (37). According to Vowles et al., an exponential increase in the use of opioids has been documented in the 20th century and a decrease in the use of opioids has been observed in the 21st century. Their chronic use marked a potential addiction, a negative impact on functioning, and subsequent withdrawal (38). Therefore, we suggest that NSAIDs and other available analgesics should be used instead of opioids to prevent such complications. The following limitations were observed: (a) a smaller number of studies were able to assess Pain score and severity effectively (b) Stevens et al. and Wilms et al. had a moderate risk of bias. Strengths of this study were: (a) enough patients were included (b) pediatrics population was also included.

6. CONCLUSION

The results of our meta-analysis and systematic review suggested an equal potential of opioids and non-opioid drugs in the management of AP. No statistical difference was observed in adverse effects, pain severity, use of an additional drug, the length of hospital stays, and mortality in adult as well as pediatric population. The major adverse effects associated with opioids were nausea, vomiting, and a short episode of hypotension.

- **Author's contribution**: The all authors were involved in all steps of preparation this article. Final profreading was made by the first author.
- **Conflicts of interest**: There are no conflicts of interest.
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