Online Resource 1: Methodological Details

The association between pain, analgesia, and delirium among critically ill adults: A Systematic Review and Meta-Analysis

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Definitions

Definitions for exposure:

No clinically significant pain was defined as no to mild pain. Clinically significant pain was defined as moderate to severe pain. Pain scores were categorized per previous research as no clinically significant pain (numeric rating scale 0-4, behavioural pain scale 3-4, or critical care pain observation tool (CPOT) 0-2) or clinically significant pain (which comprised moderate pain (numeric rating scale 5-6, behavioural pain scale 5-7, or CPOT 3-4), or severe pain (numeric rating scale ≥ 7, behavioural pain scale ≥8, or CPOT ≥ 5)) (1, 17). Pain severity was defined per the rating tool used in the published study.

Opioid classification was: (1) fentanyl; (2) morphine; (3) opioids not otherwise specified; and (4) miscellaneous opioids, including hydromorphone, methadone, meperidine, and pethidine. Non-opioid classification was: (1) ketamine; (2) dexmedetomidine; (3) tramadol; (4) acetaminophen; and (5) non-steroidal anti-inflammatories.

Definitions for outcome:

Delirium was dichotomized as present or absent per the rating tool used in the published study. Delirium presence was defined as Richmond agitation sedation scale (RASS) -3 or higher and one of intensive care delirium screening checklist (ICDSC) ≥ 4 out of 8, or confusion assessment method in the ICU (CAM-ICU) with acute change in mental status (Feature 1), and inattention (Feature 2), and one of disorganised thinking (Feature 3) or altered level of consciousness (Feature 4) (14, 17). Other tools that were validated in critically ill patients for the diagnosis of delirium were accepted, including: variations of the CAM-ICU (such as CAM-ICU-7 or CAM-Severity), organic brain syndrome, and Neelon and Champagne confusion scale (18, 19). We included studies that used chart review or did not specify the tool used to define delirium.

Delirium severity was defined per the rating tool used in the published study. For ICDSC, delirium is absent (ICDSC 0), subsyndromal (ICDSC 1-3), or present (ICDSC 4-8) (18). For CAM-Severity, higher scores indicate more severe delirium (short form is scored out of 7, and long form is scored out of 19). For CAM-ICU-7, delirium is absent (CAM-ICU-7 0 – 2), mild to moderate (CAM-ICU-7 3-5), or severe (CAM-ICU-7 6-7) (18). For CAM-Severity, higher scores indicate more severe delirium (short form is scored out of 7, and long form is scored out of 19).

Due to the heterogeneity of inclusion criteria among included studies, we chose to present delirium occurrence rather than delirium prevalence. Individual studies did not consistently exclude patients with delirium at baseline, and there was heterogeneity in delirium definitions.

Search Strategy

Conferences in which authors hand-searched abstracts: Society of Critical Care Medicine Annual Congress, American Thoracic Society International Conference, European Society of Intensive Medicine Annual Congress, the Canadian Critical Care Forum, and the American Delirium Society Annual Conference.

Where the same cohort of subjects was reported in multiple publications, only unique findings were presented grouped together such that data included in the final analysis was reported from one source.

Full inclusion and exclusion criteria:
Studies were included if they were randomised controlled trials, non-randomised quasi-experimental, cohort, case control, or secondary analyses of these designs; adults were defined as at least 18 years of age; admitted to any ICU; for which we were able to extract data on reports of pain or exposure to analgesics while admitted to the ICU; and reported delirium incidence, prevalence or severity. We excluded studies that were non-original research, case reports or case series; animal or laboratory studies; studies only reporting alcohol withdrawal delirium, substance withdrawal delirium, delirium tremens or emergence delirium; non-pharmacologic methods as the primary method of pain management; observational trials that only presented data for analgesics in combination with a benzodiazepine; and randomised controlled trials that compared analgesics to analgesics combined with benzodiazepines.

Study selection process:
Prior to the full-text review stage, the eligibility criteria were pilot tested, with an interobserver reliability cut-off of at least κ=0.8.
Google Translate was used to handle studies written in a language other than English (17). A PRISMA flowchart was used to document steps in citation screening and final study inclusion.

Data extraction:
Variables that were extracted included: study year, date of publication, ICU type (i.e., general (mixed medical-surgical), surgical, medical, trauma, mixed), country, inclusion and exclusion criteria, number of patients, definition of pain and delirium, age, severity of illness, proportion female sex, opioids (drug, class, dose), non-opioid analgesics (drug, class, dose), pain scores, delirium scores, and delirium duration.

Statistical Analysis:
Our secondary analysis examined the severity of pain and delirium.

Opioids were analysed in the following order: (1) fentanyl; (2) morphine; (3) opioids not otherwise specified; and (4) miscellaneous opioids, including hydromorphone, methadone, and meperidine. For the morphine-delirium association, data from the Rahimi-Bashar et al (21) study did not converge using the Peto method and were excluded from analysis.

Non-opioids were analysed in the following order: (1) ketamine; (2) dexmedetomidine; (3) tramadol; (4) acetaminophen; (5) non-steroidal anti-inflammatories.

An I^2 less than 25% was considered as no heterogeneity, 25% to 50% as low heterogeneity, 51% to 75% as moderate heterogeneity, and greater than 75% as high heterogeneity (18).