**Supplemental Table 3. Pain Group Evidence Summaries and Evidence to Decision Tables**

**Question**: Adjunctive nefopam compared to no adjunctive nefopam for ICU pain management (5.2)

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **adjunctive nefopam** | **no adjunctive nefopam** | **Relative (95% CI)** | **Absolute (95% CI)** |
| VAS Score with movement | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | serious b | serious c | none | Overall no difference in Pain assessment with or without nefopam: at rest and during movement at 12, 24, 36, 48 and 72 h after surgery using a visual analogue scale (VAS) Pain with movement at 48h was the only time point for which the difference was statistically significant. All others were non-significant. | | | | ⨁◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. Randomization method not described, no intention to treat with 24/300 loss to follow-up, blinding described

b. Only included CVICU patients in this study, however analgesic efficacy may be broadly applicable to all ICU patients

c. Confidence Intervals do not cross z ero (no effect) - however small sample siz e hard to draw conclusion on nefopam effects

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| **Question** | | | |
| Should **adjunctive nefopam** vs. **no adjunctive nefopam** be used for **ICU pain management (5.2)**? | | | |
| **Population:** | ICU pain management (5.2) | **Background:** |  |
| **Intervention:** | adjunctive nefopam |
| **Comparison:** | no adjunctive nefopam |
| **Main outcomes:** | VAS Score with movement; |
| **Setting:** |  |
| **Perspective:** |  |

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ○ No ○ Probably no ○ Probably yes ● Yes  ○ Varies ○ Don't know | It is top priority to investigate the effectiveness/side effects of Adjunctive Non opioid analgesics to opioids compared to opioids alone in order to decrease opioids related side effects that are especially at risk in ICU patients:  - respiratory depression  - neurological impairment (decreased vigilance, delirium)  - ileus, nausea vomiting, etc...  **Kim et al. 2014 [1]**  n=276 patients scheduled to undergo cardiac surgery were randomly assigned between three  PCA groups (92 patients per group): nefopam, fentanyl or nefopam + fentanyl.  Each drug was given continuously + in PCA mode.  *NB (1): For Question 5.2, we only take into consideration nefopam+fentanyl group versus fentanyl group.*  **Pain assessment:**  at rest and during movement  at 12, 24, 36, 48 and 72 h after surgery using a visual analogue scale (VAS)  *NB (2): The evidence table reported only pain at H48 which was the only time point for which the difference was statistically significant.* | **Doses:**  *nefopam group:*  nefopam 4 mg/h  bolus: nefopam 2 mg (lock out ime = 15 min)    *fentanyl group:*  fentanyl 20 µg/h  bolus: fentanyl 10 µg (lock out ime = 15 min)    *nefopam+fentanyl group:*  nefopam 1.86 mg/h + fentanyl 9.4 µg/h  bolus: nefopam 0.93 mg + fentanyl 4.7 µg    (lock out ime = 15 min in every group) |
| Desirable Effects | **How substantial are the desirable anticipated effects?**  ○ Trivial ● Small ○ Moderate ○ Large  ○ Varies ○ Don't know | This study has a **"Non inferiority design"**  According to the study design, there was no inferiority of nefopam (adjunctive or not) compared to fentanyl (VAS non significant at H24 at rest and during movement).  *Note that fentanyl dose changes according to the group from 0 (no fentanyl, nefopam only) to 9.4 µg/h (nefopam+fentanyl group) to 20 µg/h (fentanyl only)*  VAS also non significant at H12, 24, 36, 48, 72 at rest, as well as during movement at H12, 24, 36, 72.  The VAS difference between group is only significant during movement at H48:  MD **0.34 higher** (0.01 higher to 0.67 higher)  i.e. VAS higher in nefopam+fentanyl group compared to fentanyl alone group | **"large" desirable anticipated effects** because nefopam did as well as fentanyl, a good point for nefopam if we would like to spare opioids. |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**  ○ Large ○ Moderate ● Small ○ Trivial  ○ Varies ○ Don't know | **"small" undesirable anticipated effects**  beucause on the contrary, nausea was less frequent in the nefopam+fentanyl group (13%) compared to the fentanyl group (27%), p<0.01 taking into account the three groups (nefopam, nefopam+fentanyl, fentanyl).  No significant difference between groups for: tachycardia, sweating, sedation, dyspnoa, prutirus, vomiting.  (All adverse events were reported during the first 48 hours).  No post-hoc tests comparing groups in pairs. |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**  ○ Very low ● Low ○ Moderate ○ High  ○ No included studies | n=92 patients per group is a small group for John Centofanti.  There was an important ROB:  Randomization method not described, no intention to treat with 24/300 loss to follow-up  Reasons for non completion of the study:  -duration of intubation > or = 48h: n=11 (it is not precised the timing of begining of the PCA with continuous mode, only that ot was "initiated postoperatively")  -repeat surgery within 72h: n=5  -reintubation in ICU: n=4  -malfunctionning PCA device: n=4 | **"low" certainty of the evidence of effects because of:**  - a moderate to important size (almost 100!)  - a double blinded design  but  - only one study  - with an important ROB |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**  ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes | Except for nausea, other classical opioid related side effects were not decreased nor investigated (respiratory rate, ileus, delirium...). | **"Possibly" important uncertainty or variability** |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention  ○ Varies ○ Don't know | Globally no statistical difference (or small difference) of pain intensity but less nausea in nefopam+fentanyl group (intervention) compared to fentanyl alone group (comparison).    Also, there is at least a 50% reduction in fentanyl dose in the nefopam+fentanyl group (see dosing above, no difference in PCA volume between groups). | **"the balance between desirable and undesirable effects favors the intervention"** |
| Resources required | **How large are the resource requirements (costs)?**  ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings  ○ Varies ○ Don't know | Nefopam costs are very small in France (20 mg = $0.39; between $1.56 and $2.34 per day usually, 2016 prices in Montpellier Hospitals) but must probably depend on the country.  Not available in the US and Canada.  Countries where nefopam was available in 2010:  BAHRAIN *- TABLETS ONLY*  BELGIUM  CHILE  DOMINICAN REPUBLIC  EGYPT  EQUATOR *- TABLETS ONLY*  FRANCE  GERMANY *- TABLETS ONLY*  HAITI  HONG KONG *- TABLETS ONLY*  IRLAND  LUXEMBOURG  MALAISIA  MALTA  MAURITIUS  MEXICO  NEW ZEALAND *- TABLETS ONLY*  OMAN  PAKISTAN  PANANA  QATAR  SALVADOR  SINGAPOUR *- TABLETS ONLY*  SWITZERLAND  THE BARBADOS *- TABLETS ONLY*  UNITED ARAB EMIRATES  UNITED KINGDOM | **"moderate costs"**  because this study used a PCA device but not the drug costs |
| Certainty of evidence of required resources | **What is the certainty of the evidence of resource requirements (costs)?**  ○ Very low ● Low ○ Moderate ○ High | Cost and availability not known in every country | See above. |
| Cost effectiveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies | PCA was used in the two groups (no increased costs related to the PCA that was used in the two groups).  Regarding the drug: nefopam might be less or more expensive than fentanyl (depends on local costs).  Also to take into consideration, if nausea is less frequent, antiemetic drugs should be less required for rescue (this should decrease the averall cost of the drugs).  *NB: ramosetron was systematically given in both groups to reduce nausea.* | **cost-effectiveness "probably" favors the intervention** |
| Equity | **What would be the impact on health equity?**  ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased |  |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies |  | **the intervention is acceptable to key stakeholders "Probably YES"**  However, this requires patient's acceptation based on her/his preference:  - some patients prefer avoiding opioids because of a past experience of nausea  - some patients prefer, or do not prefer, using a PCA device |
| Feasibility | **Is the intervention feasible to implement?**  ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know | Nefopam is widely available but not in all countries  (please, see the countries where nefopam is available above). | **"Varies"** |

**Summary of judgements**

|  | **Judgement** | | | | | | | **Implications** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |  |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |  |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |  |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |  |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  | No known undesirable outcomes |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |  |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |  |
| **Certainty of evidence of required resources** | Very low | **Low** | Moderate | High |  |  | No included studies |  |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | No included studies |  |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |  |
| **Acceptability** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |  |
| **Feasibility** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |  |

**Should adjunctive nefopam vs. no adjunctive nefopam be used for ICU pain management (5.2)?**

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| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ○ | ● | ○ | |
| **Recommendation** | We suggest that adjunctive nefopam (if available) can be used to decrease opioid dose and nausea while treating pain in ICU patients (at risk of opioid side effects) (+2C).  no recommendation  nausea considered in previous recommendation comparing nefopam vs fentanyl groups; no clinical outcomes difference, reduction in side effects |
| **Justification** | **Overall justification**  Only one moderate size, moderate quality (8% of excluded patients, no intent to treat analysis) doube blind RCT in 184 postcardiac SICU patients able to use a PCA device.  -> Level B of evidence because the RCT is downgraded.  **Detailed justification**  *Problem*  Very selected ICU population. However, generalization of the results to another kind of population is likely because pain is frequent in postcardiac SICU patients.  *Feasibility*  Patients able to use a PCA device. These promising results need to be also found in patients unable to use a PCA device (non communicant patients). However, 62% of nefopam +fentanyl infusion was provided continuously (not by PCA) at H12, and 77% at H48. |
| **Subgroup considerations** |  |
| **Implementation considerations** | Availability of nefopam in some countries, availability of a PCA device in some ICUs. |
| **Monitoring and evaluation** | Analgesic related side effects or outcomes should be assessed more largely including:  -delirium  -ileus  -duration of MV weaning  -LOS in ICU and hospital |
| **Research priorities** | This is top priority to investigate adjunctive analgesics that could decrease opioids dose to treat pain in ICU patients.  These promising results require that this study be replicated:  - in medical ICU and noncardiac SICU patients  - non communicant patients  - using a more common mode of drug administration in ICU patients who are sometimes non communicant (a continuous infusion with boli and/or an intermittent administration, but provided by the nurse based on behavioral pain tools, instead of a PCA device needing the participation of the patient) |
| **comments during electronic Voting by Entire panel** | Adding nefopam did not appear to change pain over time; do lower fentanyl doses translate into clinical benefit?  Nausea (side effect) has a risk of bias in this specific population; Inexperience using this medication mitigates enthusiasm  Rephrazing to consider nefopam alone vs opioid alone: should adjunctive nefopam or nefopam alone (vs. an opioid alone) be used…?  Very low quality of evidence, how can a decision be stated? |

**Question**: Nefopam compared to Opioids for ICU Patients (5.1)

**Setting**: Post-operative Cardiac Surgery Patients

**Bibliography**: Kim K., Kim WJ., Choi DK., Lee YK, Choi I., Sim J. The analgesic efficacy and safety of nefopam in patient-controlled analgesia after cardiac surgery: A randomized, double-blind, prospective study. Journal of International Medical Research: 42(3), 684-692.

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Nefopam** | **Opioids** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain at rest at 24 hours (follow up: mean 24 Hours; assessed with: Visual Analogue Scale; Scale from: 0 to 10) | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | not serious b | serious c | none | 92 | 92 | - | mean **0.23 mean higher** (0.21 lower to 0.68 higher) | ⨁⨁◯◯ LOW | IMPORTANT |
| Pain with movement at 24 hours (follow up: mean 24 hours; assessed with: Visual Analogue Scale; Scale from: 0 to 10) | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | not serious b | serious c | none | 92 | 92 | - | mean **0.14 mean higher** (0.28 lower to 0.56 higher) | ⨁⨁◯◯ LOW | IMPORTANT |
| Pain at rest at 48 hours (assessed with: Visual Analogue Scale) | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | not serious b | serious c | none | 92 | 92 | - | MD **0.25 higher** (0.553 lower to 0.053 higher) | ⨁⨁◯◯ LOW | IMPORTANT |
| Pain with movement at 48 hours (follow up: mean 24 hours; assessed with: Visual Analogue Scale; Scale from: 0 to 10) | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | not serious b | serious c,d | none | 92 | 92 | - | MD **0.41 higher** (0.081 higher to 0.739 higher) | ⨁⨁◯◯ LOW | IMPORTANT |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. Randomization method not described, no intention to treat with 24/300 loss to follow-up, blinding described

b. Only included CVICU patients in this study, however analgesic efficacy may be broadly applicable to all ICU patients

c. Large confidence intervals, cannot determine if value of nefopam independently

d. Confidence Intervals do not cross zero (no effect) - however small sample size hard to draw conclusion on nefopam effects

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| **Question** | | | |
| Should **Nefopam** vs. **Opioids** be used for **ICU Patients (5.1)**? | | | |
| **Population:** | ICU Patients (5.1) | **Background:** |  |
| **Intervention:** | Nefopam |
| **Comparison:** | Opioids |
| **Main outcomes:** | Pain at rest at 24 hours; Pain with movement at 24 hours; Pain at rest at 48 hours; Pain with movement at 48 hours; |
| **Setting:** | Post-operative Cardiac Surgery Patients |
| **Perspective:** |  |

**Assessment**

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| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ○ No ○ Probably no ○ Probably yes ● Yes  ○ Varies ○ Don't know | It is top priority to investigate the effectiveness/side effects of Non opioid analgesics compared to opioids in order to decrease opioids related side effects that are especially at risk in ICU patients:  - respiratory depression  - neurological impairment (decreased vigilance, delirium)  - ileus, nausea vomiting, etc...  **Kim et al. 2014[1]**  n=276 patients scheduled to undergo cardiac surgery were randomly assigned between three  PCA groups (92 patients per group): nefopam, fentanyl or nefopam + fentanyl.  Each drug was given continuously + in PCA mode.  *NB (1): For Question 5.1, we only take into consideration nefopam group versus fentanyl group.*  **Pain assessment:**  at rest and during movement  at 12, 24, 36, 48 and 72 h after surgery using a visual analogue scale (VAS)  *NB (2): The evidence table reported only pain at rest and with movement at H24 and H48.* | **Doses:**  *nefopam group:*  nefopam 4 mg/h  bolus: nefopam 2 mg (lock out ime = 15 min)  *fentanyl group:*  fentanyl 20 µg/h  bolus: fentanyl 10 µg (lock out ime = 15 min)  *nefopam+fentanyl group:*  nefopam 1.86 mg/h + fentanyl 9.4 µg/h  bolus: nefopam 0.93 mg + fentanyl 4.7 µg  (lock out ime = 15 min for every group) |
| Desirable Effects | **How substantial are the desirable anticipated effects?**  ○ Trivial ● Small ○ Moderate ○ Large  ○ Varies ○ Don't know | This study has a "Non inferiority design"  According to the study design, there was no inferiority of nefopam compared to fentanyl  (VAS non significant at H24 at rest and during movement).  VAS also non significant at H12, 24, 36, 48, 72 at rest, as well as during movement at H12, 24, 36, 72.  The VAS difference between group is only significant during movement at H48:  MD **0.41 higher** (0.081 higher to 0.739 higher)  i.e. VAS higher in nefopam group compared to fentanyl group | **"large" desirable anticipated effects** because nefopam did as well as fentanyl, a good point for nefopam if we would like to spare opioids.  Is nefopan better than opioids? Different approach from the one we used in previous questions. Small effect.  -agrees; large would mean that nefopam is better than opioids; small  -agrees with small  Group consensus for "small effects" |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**  ○ Large ○ Moderate ● Small ○ Trivial  ○ Varies ○ Don't know | **"small" undesirable anticipated effects** because on the contrary,  nausea was less frequent in the nefopam group (11%) compared to the fentanyl group (27%), p<0.05.  -No significant difference between groups for:  tachycardia, sweating, sedation, dyspnea, prutirus, vomiting. (All adverse events were reported during the first 48 hours).  -could be moved to moderate conisdeing that they were fewer side effects with nefopam; are their adverse effects of nefopam that could be detrimental?  -delirium (but not reported)  -curious to know how they found out about nausea in MV patients: moderate or small would be fine  -small because the difference is not large between the 2 groups  nefopam has small undesirable effects compare to opioids |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**  ○ Very low ● Low ○ Moderate ○ High  ○ No included studies | n=92 patients per group is a **small group** for John Centofanti. **There was an important ROB:**  Randomization method not described, no intention to treat with 24/300 loss to follow-up *Reasons for non completion of the study:*  *-duration of intubation > or = 48h: n=11 (it is not precised the timing of begining of the PCA with continuous mode, only that ot was "initiated postoperatively")*  *-repeat surgery within 72h: n=5*  *-reintubation in ICU: n=4*  *-malfunctionning PCA device: n=4* | **"moderate" certainty of the evidence of effects because of:**  - a moderate to important size (almost 100!)  - a double blinded design  but  - only one study  - with an important ROB  - imprecision noted (CI) + ROB assessment  - Low because only one study; power analysis missing; non-significant results  Group: keep "low" |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**  ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability  ○ No known undesirable outcomes | Except for nausea, other classical opioid related side effects were not decreased nor investigated (respiratory rate, ileus, delirium...). | **"Possibly" important uncertainty or variability**  **In previous questions, we referred to pain scores as the main outcome. VAS is a valid and accepted measure.** |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know | Globaly no statistical difference (or small difference) of pain intensity but less nausea in nefopam group (intervention) compared to fentanyl group (comparison). | **Gerald: "the balance between desirable and undesirable effects favors the intervention" because:**  **-Probably favors because the only difference was for nausea; only one study too**  - **balancing between nefopam and opioids**  -**also consider the possibility to reduce exposure to opioids** |
| Resources required | **How large are the resource requirements (costs)?**  ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings  ○ Varies ○ Don't know | Nefopam costs are very small in France (20 mg = $0.39; between $1.56 and $2.34 per day usually, 2016 prices in Montpellier Hospitals) but must probably depend on the country.    Not available in the US and Canada.  Countries where nefopam was available in 2010:  See above for list of countries where marketed | **"moderate costs"**  because this study used a PCA device but not regarding the drug costs |
| Certainty of evidence of required resources | **What is the certainty of the evidence of resource requirements (costs)?**  ○ Very low ● Low ○ Moderate ○ Higg ○ No included studies |  | See above. |
| Cost effectiveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies | PCA was used in the two groups (no increased costs related to the PCA that was used in the two groups).  Regarding the drug: nefopam might be less or more expensive than fentanyl (depends on local costs).  Also to take into consideration, if nausea is less frequent, antiemetic drugs should be less required for rescue (this should decrease the averall cost of the drugs).  *NB: ramostron was systematically given in both groups to reduce nausea.* | **cost-effectiveness "probably" favors the intervention** |
| Equity | **What would be the impact on health equity?**  ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know |  | **intervention is acceptable to key stakeholders "Probably YES"**  because this requires patient's acceptation based on her/his preference:  - some patients prefer avoiding opioids because of a past experience of nausea for example  - some patients prefer, or do not prefer, using a PCA device  **It varies because of the availability of the drug and the use of PCA.**  **Varies because also depends on patient's preference.** |
| Feasibility | **Is the intervention feasible to implement?**  ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know | Nefopam is widely available but not in all countries (Canada and the US for example... but these guidelines are international :) | **"varies"** |

**Summary of judgements**

|  | **Judgement** | | | | | | | **Implications** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |  |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |  |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |  |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |  |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  | No known undesirable outcomes |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |  |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |  |
| **Certainty of evidence of required resources** | Very low | **Low** | Moderate | High |  |  | No included studies |  |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | No included studies |  |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |  |
| **Acceptability** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |  |
| **Feasibility** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |  |

**Should Nefopam vs. Opioids be used for ICU Patients (5.1)?**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ● | ○ | ○ | |
| **Recommendation** | We suggest that nefopam (if available) can be an alternative to opioids to treat pain in ICU patients, especially in case of opioids contraindication (+2C).  Change "might" with "can"; keep it general and specify in the justification the sub-group considerations. |
| **Justification** | **Overall justification**  Only one moderate size, moderate quality (8% of excluded patients, no intent to treat analysis) doube blind RCT in 184 postcardiac SICU patients able to use a PCA device.  -> Level B of evidence because the RCT is downgraded.  **Detailed justification**  *Problem*  Very selected ICU population. However, generalization of the results to another kind of population is likely because pain is frequent in postcardiac SICU patients.  *Feasibility*  Patients were able to use a PCA device. These promising results need to be also found in patients unable to use a PCA device (non communicant patients). However, 63% of nefopam infusion was provided continuously (not by PCA) at H12, and 83% at H48. |
| **Subgroup considerations** | Cardiac surgery patients |
| **Implementation considerations** | Availability of nefopam in some countries, availability of a PCA device in some ICUs. |
| **Monitoring and evaluation** | Analgesic related side effects or outcomes should be assessed more largely including:  -delirium  -ileus  -duration of MV weaning  -LOS in ICU and hospital |
| **Research priorities** | This is top priority to investigate alternative analgesics to opioids to treat pain in ICU patients.  These promising results require that this study be replicated:  - in medical ICU and noncardiac SICU patients/ - non-communicative patients  - using a more common mode of drug administration in ICU patients who are challenged when communicating (e.g. a continuous infusion with boluses and/or an intermittent administration, provided by the nurse based on behavioral pain tools, instead of a PCA device needing the participation of the patient) |
| **comments during electronic Voting by Entire panel** | Nefopam of uncertain benefit for pain given no change at most time points- despite non-inferiority trial. Although fentanyl dose lower, how did that translate into a clinical benefit? Nausea finding has risk of bias (specific patient population); Limited applicability to US.  Rephrazing to consider nefopam alone vs opioid alone: adjunctive nefopam or nefopam alone (vs. an opioid alone) be used…? Should we consider this opiate-sparing strategy? Very low quality of evidence, how can a decision be stated? Inexperience using this medication mitigates enthusiasm |

**Question**: Adjunctive paracetamol compared to no adjunctive paracetamol for ICU pain management (5.2)

**Setting**: Intensive Care Unit

| **Quality assessment** | | | | | | | **№ of patients** | | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other conside-rations** | **adjunctive paracetamol** | **no adjunctive paracetamol** | | **Relative (95% CI)** | **Absolute (95% CI)** |
| VAS Score at 24 hours postoperatively (in cm) | | | | | | | | | | | | | |
| 2 | randomised trials | serious a | not serious | not serious b | not serious | none | 76 | 77 | | - | MD **0.46 lower** (0.69 lower to 0.23 lower) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Mean BPS Pain Scores until patient extubated | | | | | | | | | | | | | |
| 1 | randomised trials | very serious c | not serious | not serious d | serious e | none | 20 | 20 | | - | MD **1.98 lower** (2.98 lower to 0.98 lower) | ⨁◯◯◯ VERY LOW | CRITICAL |
| Pain Score at extubation | | | | | | | | | | | | | |
| 1 | randomised trials | very serious c | not serious | not serious d | serious e | none | 20 | 20 | | - | MD **1.1 lower** (1.73 lower to 0.47 lower) | ⨁◯◯◯ VERY LOW | CRITICAL |
| Time to extubation (minutes) | | | | | | | | | | | | | |
| 1 | randomised trials | very serious c | not serious | not serious d | serious e | none | 20 | 20 | | - | MD **140.2 lower** (192.7 lower to 87.7 lower) | ⨁◯◯◯ VERY LOW | CRITICAL |
| Rescue Doses of Morphine | | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious f | serious g | none | 8/56 (14.3%) | 14/57 (24.6%) | | OR 0.51 (0.20 to 1.34) | **103 fewer per 1,000** (from 58 more to 184 fewer) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Opioid Consumption (in Morphine equivalents) | | | | | | | | | | | | | |
| 2 | randomised trials | serious a | not serious | not serious b | not serious | none | 76 | | 77 | - | MD **4.54 lower** (6.6 lower to 2.47 lower) | ⨁⨁⨁◯ MODERATE | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference; **OR:** Odds ratio

#### Explanations a. 1 study has low ROB, however the 2nd study was high ROB due to lack of blinding, no intention to treat and unclear randomization process b. Includes both postoperative cardiac surgery and abdominal surgery patients c. No blinding, unclear randomization process, no intention to treat

d. Includes only abdominal surgery ICU pts. Lowered due to very small sample size f. Includes only cardiac surgery ICU patients g.OR CI cannot rule out harm at upper limit

|  |  |  |  |
| --- | --- | --- | --- |
| **Question** | | | |
| Should **adjunctive paracetamol** vs. **no adjunctive paracetamol** be used for **ICU pain management (5.2)**? | | | |
| **Population:** | ICU pain management (5.2) | **Background:** |  |
| **Intervention:** | adjunctive paracetamol |
| **Comparison:** | no adjunctive paracetamol |
| **Main outcomes:** | VAS Score at 24 hours postoperatively (in cm); Mean BPS Pain Scores until patient extubated; Pain Score at extubation; Time to extubation (minutes); Rescue Doses of Morphine; Opioid Consumption (in Morphine equivalents); |
| **Setting:** | Intensive Care Unit |
| **Perspective:** |  |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ○ No ○ Probably no ○ Probably yes ● Yes  ○ Varies ○ Don't know | It is top priority to investigate the effectiveness/side effects of Adjunctive Non opioid analgesics to opioids compared to opioids alone in order to decrease opioids related side effects that are especially at risk in ICU patients:  - respiratory depression  - neurological impairment (decreased vigilance, delirium)  - ileus, nausea vomiting, etc...  Two single center RCT in ICU patients after a scheduled surgery  **- Cattabriga 2007 [2]:** cardiac surgery, n=113, low ROB  **- Memis 2010 [3]:** abdominal surgery, n=40, unblinded, high ROB  **Intervention:**  Adjunct IV paracetamol 1g/6hrs in both studies  - Cattabriga [2]: **for 72 hours**, opioid= tramadol + rescue morphine  - Memis [3]: **for 24 hours**, opioid= mepiridine + rescue mepiridine  **Pain measurement:**  VAS in Cattabriga [2] (/6h till H72, at rest and during deep breath),  mean VAS after extubation in Memis (at H24 postextubation);  mean BPS before and at extubation in Memis |  |
| Desirable Effects | **How substantial are the desirable anticipated effects?**  ○ Trivial ○ Small ● Moderate ○ Large  ○ Varies ○ Don't know | **Mean BPS before extubation** (Memis) [3] : MD 3 fewer (3 fewer to 1 fewer) (5.7 versus 3.7)  **Mean BPS at extubation** (Memis) [3]: MD 1 fewer (1.7 fewer to 0.5 fewer) (3.6 versus 2.5 -> it is weird to show a result of mean BPS < 3??)  **Forrest plot for VAS (cm)** supposed to be at rest in both studies = -0.5 [-0.7 to -0.2]  In fact, Cattabriga has the highest weight (highest reduction in VAS) but no difference in opioid consumption. Inversely, there was a less important reduction of VAS in Memis [3]but a significant reduction in opioid consumption.  I think is mathematical/logical. Adjunct paracetamol has "additional" analgesic effect.  *NB: mean VAS are low in all groups in both studies* *(means or medians < 3)*  **Forrest plot for opioid consumption** (mg morphine equivalents, within 24h for Memis; 72h for Cattabriga [2]) = -4.5 [-6.6 to -2.5]  *-was the forrest plot mean the consumption per 24h or was it an "overall" forest plot taking into account the consumption within 24h in Memis and in 72h in Catabriga?*  Rescue dose of morphine (Cattabriga [2]) : OR 0.51 (0.20 to 1.34)  **Other outcomes:**  Time to extubation in minutes (Memis[3]): MD 140 fewer (193 fewer to 88 fewer)  Sedation score (1 to 5 points scale) significantly lower in Memis (= less sedated)  Nausea lower in Memis[3], Nausea NS in Cattabriga [2]  ICU LOS, respiratory depression, reintubation, pruritus: NS in Memis  Respiratory rate significantly lower in paracetamol group at H12 only in Cattabriga | **"moderate" desirable anticipated effects**  because mean VAS are low in all groups in both studies but there is a significant reduction of VAS and opioid consumption. |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**  ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know | **"small" undesirable anticipated effects**  because no adverse outcome was reported, on the contrary: decreased duration of MV and nausea in one study  Paracetamol is a safe drug if dose is appropriately given (according to patient's weight, renal insuficiency). Otherwise, there is a risk of hepatitis and renal failure. Not assessed in these studies.  Question: No adverse events reported, what about vital parameters (e.g., blood pressure)? in association with dosing  small  don't know  no differences in BP between groups in Cattabriga [2] and Memis [3]  trivial (of little value or importance)  Trivial based on information we have |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**  ○ Very low ○ Low ● Moderate ○ High ○ No included studies | Two RCTs but single center, one double blinded with a low ROB (Cattabriga) [2], one unblinded with a high ROB, that was also a very small size study (Memis) [3]. | **"moderate" certainty of the evidence** |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**  ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes |  | **"Probably no important" uncertainty or variability**  **Celine: No important uncertainty when we have solid measures of outcomes (pain scores, opioid doses)** |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  | **Probably favors the intervention**  because significant reduction in VAS and opioid consumption and probably lower rate of adverse outcomes (in the lowest quality study) |
| Resources required | **How large are the resource requirements (costs)?**  ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know | IV Paracetamol in not expensive in France (Price in Montpellier hospitals in 2016): $0.69 for 1 gramm IV ($2.76 for 4 gramms a day).  Is it the same case in the US/Canada?  Not available in Canada | **Negligible costs and savings**  because IV paracetamol is not expensive and because it is associated with savings related to reduced opioid consumption.  costs will vary based on the country |
| Certainty of evidence of required resources | **What is the certainty of the evidence of resource requirements (costs)?**  ○ Very low ○ Low ○ Moderate ○ High ● No included studies | Not addressed in the 2 RCTs |  |
| Cost effectiveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies | Not addressed in the 2 RCTs | **Probably favors the intervention** |
| Equity | **What would be the impact on health equity?**  ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | Considering all routes of administration | **"Probably YES"** |
| Feasibility | **Is the intervention feasible to implement?**  ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  | **the intervention is feasible to implement-> "YES"**  because systematic administration of paracetamol is easy to implement |

**Summary of judgements**

|  | **Judgement** | | | | | | | **Implications** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |  |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |  |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |  |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |  |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  | No known undesirable outcomes |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | **Probably favors the intervention** | Favors the intervention | Varies | Don't know |  |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | **Varies** | Don't know |  |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |  |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |  |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |  |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |  |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |  |

**Should adjunctive paracetamol vs. no adjunctive paracetamol be used for ICU pain management (5.2)?**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ○ | ● | ○ | |
| **Recommendation** | We suggest that adjunctive paracetamol might be used to decrease pain intensity and opioid consumption in ICU patients (+2C).  Remove "IV" because not part of the question; keep the recommendation general  RCTs done with IV paracetamol  IV comparable to po route of administration in previous studies |
| **Justification** | **Overall justification**  Two RCT but single centers, one of very low quality (unblinded, high ROB, small size).  -> level of evidence C because the study that showed less undesirable effects has a low quality (unblinded, hogh ROB), it was downgraded to C. The high quality study that showed the highest reduction in VAS showed also low VAS in both groups and no additional effects.  **Detailed justification**  *Problem*  Surgical ICU population (one cardiac, one abdominal, both scheduled). However, generalization of the results to another kind of population is likely because pain is frequent in SICU patients as in medical ICU patients. |
| **Subgroup considerations** | Cardiac and abdominal surgery patients |
| **Implementation considerations** | None  IV route not available in Canada, and expensive in US - but other routes can be used |
| **Monitoring and evaluation** | Pain assessment  Analgesic related side effects or outcomes should be assessed more largely including:  -delirium  -ileus  -duration of MV weaning  -LOS in ICU and hospital  Paracetamol related side effects should be assessed more specifically: increased serum liver enzymes (acute hepatitis), decreased liver and kidney function |
| **Research priorities** | This is top priority to investigate analgesics that can decrease the use or dose of opioids to treat pain in ICU patients. These promising results require that these studies be replicated:  - in medical ICU; other surgeries and trauma  - non-verbal patients (only one small size study assessed the BPS before extubation  Other routes of paracetamol administration to be investigated |
| **comments during electronic Voting by Entire panel** | with very low quality of evidence should the recommendation be as stated? or re-phrased to indicate you cannot make a recommendation? |

**Question**: Adjunctive ketamine compared to no adjunctive ketamine for ICU analgesic management (5.2)

**Setting**: Intensive Care Unit

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **adjunctive ketamine** | **no adjunctive ketamine** | **Relative (95% CI)** | | **Absolute (95% CI)** |
| Cumulative morphine consumption (follow up: mean 48 hours; assessed with: dose (mg)) | | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | serious b | not serious | none | 41 | 52 | - | MD **22 mg fewer** (14 fewer to 30 fewer) | | ⨁⨁◯◯ LOW | IMPORTANT |
| VAS score at rest (follow up: mean 48 hours; assessed with: VAS score (mm); Scale from: 0 to 100) | | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | serious b | serious c | none | 41 | 52 | - | MD **3 mm lower** (10.88 lower to 4.88 higher) | | ⨁◯◯◯ VERY LOW | CRITICAL |
| VAS score with movement (follow up: mean 48 hours; assessed with: VAS Score (mm); Scale from: 0 to 100) | | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | serious b | serious c | none | 41 | 52 | - | MD **4 mm lower** (15.02 lower to 7.02 higher) | | ⨁◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. Unclear randomization process and location concealment, no intention to treat analysis,

b. Only postoperative major abdominal surgery patients included

c. Unclear benefit, small sample size

|  |  |  |  |
| --- | --- | --- | --- |
| **Question** | | | |
| Should **adjunctive ketamine** vs. **no adjunctive ketamine** be used for **ICU analgesic management (5.2)**? | | | |
| **Population:** | ICU analgesic management (5.2) | **Background:** |  |
| **Intervention:** | adjunctive ketamine |
| **Comparison:** | no adjunctive ketamine |
| **Main outcomes:** | Cumulative morphine consumption; VAS score at rest; VAS score with movement; |
| **Setting:** | Intensive Care Unit |
| **Perspective:** |  |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | It is top priority to investigate the effectiveness/side effects of Adjunctive Non opioid analgesics to opioids compared to opioids alone in order to decrease opioids related side effects that are especially at risk in ICU patients:  - respiratory depression  - neurological impairment (decreased vigilance, delirium)  - ileus, nausea vomiting, etc...  One single center double-blinded RCT in 93 postscheduled abdominal surgery ICU patients, high ROB (unclear randomization process and location concealment, no intention to treat analysis despite 8 patients excluded after enrollment) **-> Guillou 2003 [4]**  two parallel groups:  1) morphine PCA + ketamine initial loading charge + kétamine continuous infusion  2) morphine PCA + placebo loading charge + placebo continuous infusion  *NB: intervention began after patients' awakening in the ICU*  **Pain intensity at rest at H48 (VAS in mm; 0-100):**  MD 3 mm lower (11 mm lower to 5 mm higher) -> NS  **Pain intensity at mobilization at H48 (VAS in mm; 0-100):**  MD 4 mm lower (15 mm lower to 7 mm higher) -> NS  *Note than mean VAS were small in both groups*  **Morphine consumption at H48 (mg)**  MD 22 mg fewer (30 fewer to 14 fewer)  **Side effects were NS:**  nausea, confusion, hallucinations, hypoventilation, pruritus;  Ramsay scale similar in the two groups |  |
| Desirable Effects | **How substantial are the desirable anticipated effects?**  ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know |  | **"Small desirabe anticipated effects"**  because in favour to the intervention (adjunctive ketamine) group:  - Small difference in VAS at every time points (p<0.05 only at H16, H44 at test; at H16, H20, H40 at mobilization)  - Significant but small difference in cumulative morphine consumption at each time point (every 4-hours from H4 to H48): 22mg at H48 = a mean of 11 mg/24h |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**  ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know | **"don't know undesirabe anticipated effects"**  because adverse effects that were measured were not frequent but the method for assessing confusion is not described, other adverse effects related to ketamine were not reported, such as nightmare, anxiety, and delirium. Some of the adverse effects related to opioids were not reported either: ileus |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**  ● Very low ○ Low ○ Moderate ○ High ○ No included studies | Only one single small size RCT with a high ROB: unclear randomization process and location concealment, no intention to treat analysis despite 8 patients excluded after enrollment | **low" certainty of the evidence fo the effects**  **Change with "very low" for consistency with evidence table** |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**  ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes |  | **Possibly important uncertainty or variability"** because the desirable effects are small and the undesirable effects seem to be small but under-reported: delirium should be measured with valid tools; psychodysleptic effects related to ketamine should be reported  No important uncertainty about main outcomes (pain scores, opioids) |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know |  | **"don't know if the balance between desirable and undesirable effects favor the intervention or the comparison"**  because small desirable effects but don't know about the undesirable effects |
| Resources required | **How large are the resource requirements (costs)?**  ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know | Ketamine costs are small. | **"moderate costs"**  because this study used a PCA device |
| Certainty of evidence of required resources | **What is the certainty of the evidence of resource requirements (costs)?**  ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  | See above |
| Cost effectiveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies | Not addressed in this study | **Cost-effectiveness "Does not favor either the intervention or the comparison"**  because the PCA device is used in both groups, the ketamine costs are small,the desirable effects are small, the undesirable effects are unknown |
| Equity | **What would be the impact on health equity?**  ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | **Is the intervention acceptable to key stakeholders? "-> "Probably YES"**  However, this requires patient's acceptation based on her/his preference:  - some patients prefer, or do not prefer, using a PCA device  -for some patients, ketamine may not be acceptable |
| Feasibility | **Is the intervention feasible to implement?**  ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | **implementation feasibility "varies"**  because it depends on the PCA availability; probably yes because it's feasible to implement ketamine |

**Summary of judgements**

|  | **Judgement** | | | | | | | **Implications** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |  |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |  |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | Varies | **Don't know** |  |
| **Certainty of evidence** | **Very low** | Low | Moderate | High |  |  | No included studies |  |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  | No known undesirable outcomes |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **Don't know** |  |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |  |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |  |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |  |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |  |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |  |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |  |

**Should adjunctive ketamine vs. no adjunctive ketamine be used for ICU analgesic management (5.2)?**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ● | ○ | ○ | |
| **Recommendation** | We suggest that either adjunctive ketamine along with morphine or morphine alone be used to treat postoperative pain in ICU patients (+2C).  Remove PCA. Consider meta-analysis reports in our recommendation?  utility in ICU is understudied |
| **Justification** | Only one single small size low quality RCT in ICU patients.-> level of evidence downgraded to C  **Also to take into consideration the recent reviews regarding ketamine to prevent/treat postoperative pain** ("Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in adults: a systematic review and meta-analysis of randomized trials, by Wang et al. Canadian Journal of anesthesia 2016" and "Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: systematic review and meta-analyses of randomized controlled trials with trial sequential analyses, by Assouline et al. Pain december 2016). Authors’ conclusions are pretty different: 1) Wang, CJA/JCA 2016 [5]  Adding ketamine to morphine/hydromorphone PCA provides a small improvement in postoperative analgesia while reducing opioid requirements. Adjunctive ketamine also reduces postoperative nausea and vomiting without a detected increase in other adverse effects; however, adverse events were probably underreported. 2) Assouline, Pain 2016 [6]  Trial sequential analyses confirmed the significant benefit of ketamine on pain intensity, cumulative morphine consumption, and postoperative nausea and vomiting and its inability to double the risk of hallucination. The available data did not allow us to make a conclusion on respiratory adverse events or to establish dose-responsiveness. |
| **Subgroup considerations** | abdominal surgery |
| **Implementation considerations** | Availability of a PCA device in some ICUs. |
| **Monitoring and evaluation** | Analgesic related adverse effects or outcomes should be assessed more largely including:  -delirium assessed with validated tools for ICU patients  -psychodysleptic effects related to ketamine (hallucinations, delusion, nightmare, anxiety...)  -ileus  -duration of MV weaning  -LOS in ICU and hospital |
| **Research priorities** | This is top priority to investigate analgesics that can decrease the use or dose of opioids to treat pain in ICU patients. There is only one negative study in postoperative abdominal surgery ICU patients. Recent updated reviews (2016) of trials investigating the effect of adjunctive ketamine to opioids administered with PCA to treat postoperative pain show a significant reduction in pain intensity, opioid consumption, nausea/vomiting. Other side effects like delirium could have been under reported. Future studies are required:  - in medical ICU patients experiencing severe pain at rest (pancreatitis for example)  - in medical and surgical ICU patients, especially non communicant patients at the early stage of sedation-analgesia, via a continuous infusion of ketamine without the need of a PCA  -patient's preference and satisfaction with ketamine  -other RCTs necessary in an ICU context |
| **comments during electronic Voting by Entire panel** | Where is the level of evidence? Broad recommendation for post-op. pain in one study with high ROB; no guidance to clinicians on when it might be (in)appropriate.  Primary ketamine infusions for sedation and analgesia? need to be clear this is not a first line therapy…  Our "suggest" recommendation could change clinician's practice given growing interest in ketamine. Caution: high risk of bias in the single study & the most important psychiatric side effects of ketamine is unreported. Need clinical benefits beyond reduced opioid consumption, psychiatric side effect analysis, good sample and low ROB. |

**Question**: Adjunct neuropathic agent compared to no adjunct neuropathic drug for ICU pain management (5.2)

**Setting**: Medical and Surgical ICUs

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **adjunct neuropathic agent** | **no adjunct neuropathic drug** | **Relative (95% CI)** | | **Absolute (95% CI)** |
| # of patients with VRS >=2/4, 10 hours post-extubation | | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | not serious b | serious c | none | 3/29 (10.3%) | 12/31 (38.7%) | **RR 0.27** (0.08 to 0.85) | | **283 fewer per 1,000** (from 58 fewer to 356 fewer) | ⨁⨁◯◯ LOW | CRITICAL |
| Opioid consumption in first 24 hours (morphine equivalent) | | | | | | | | | | | | | |
| 4 | randomised trials | serious d | not serious | not serious | not serious | none | 97 | 97 | - | | MD **13.54 lower** (14.57 lower to 12.5 lower) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Time to Extubation (hours) | | | | | | | | | | | | | |
| 2 | randomised trials | serious a | not serious | not serious b | serious e | none | 49 | 51 | - | | MD **0.36 higher** (0.7 lower to 1.43 higher) | ⨁⨁◯◯ LOW | CRITICAL |
| ICU LOS | | | | | | | | | | | | | |
| 2 | randomised trials | serious a | not serious | not serious b | serious f | none | 49 | 51 | - | MD **0.04 lower** (0.46 lower to 0.38 higher) | | ⨁⨁◯◯ LOW | CRITICAL |
| NRS Score Day 4 after Neuropathic Agent initiated | | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | not serious g | not serious | none | 42 | 30 | - | MD **3.44 lower** (3.9 lower to 2.98 lower) | | ⨁⨁⨁⨁ HIGH | CRITICAL |
| Breakthrough pain in first 48hrs (average #/pt) | | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | serious e | none | 20 | 20 | - | MD **1.45 lower** (2.13 lower to 0.77 lower) | | ⨁⨁⨁◯ MODERATE | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

#### Explanations a. Unclear randomization process, no intention to treat with 10 patients excluded from analysis post-randomization b. Only includes cardiac surgery patients c. Low event-rate d. Unclear randomization, no intention to treat e. Small sample size

f. Unclear if any benefit or harm g. Only includes patients with Guillain Barre

|  |  |  |  |
| --- | --- | --- | --- |
| **Question** | | | |
| Should **adjunct neuropathic agent** vs. **no adjunct neuropathic drug** be used for **ICU pain management (5.2)**? | | | |
| **Population:** | ICU pain management (5.2) | **Background:** |  |
| **Intervention:** | adjunct neuropathic agent |
| **Comparison:** | no adjunct neuropathic drug |
| **Main outcomes:** | # of patients with VRS >=2/4, 10 hours post-extubation; Opioid consumption in first 24 hours (morphine equivalent); Time to Extubation (hours); ICU LOS; NRS Score Day 4 after Neuropathic Agent initiated; Breakthrough pain in first 48hrs (average #/pt); |
| **Setting:** | Medical and Surgical ICUs |
| **Perspective:** |  |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | It is top priority to investigate the effectiveness/side effects of Adjunct Non opioid analgesics to opioids compared to opioids alone in order to decrease opioids related side effects that are especially at risk in ICU patients:  - respiratory depression  - neurological impairment (decreased vigilance, delirium)  - ileus, nausea vomiting, etc...  Also, opioids are not very effective to treat neuropathic pain compared to more specific analgesics (antineuropathic agents). If nociceptive pain is probably the most frequent mechanism of pain in ICU patients (medical, surgical illness and trauma; nociceptive care procedures), some patients can experiment a typical neuropathic pain as patients hospitalized in ICU for a Guillain-Barré syndrome.  Four single center double blinded RCTs:  **Patients with Guillain-Barré syndrome : 2 RCTs**  Pandey 2002 [7](cross over design, n=18), Pandey 2005[8] (parallel groups, n=12 x 3)  **ICU patients admitted after elective cardiac surgery : 2 RCTs**  Pesonen 1997 [9] (parallel groups, n=29 vs n=31)  Joshi 2013 [10] (parallel groups, n=20 vs n=20)  **Drugs:**  Gabapentin vs. placebo (Pandey 2002) [7]  Gabapentin vs. Carbamazepine vs. placebo (Pandey 2005) [8]  Pregabalin vs. placebo (Pesonen 1997, Joshi 2013) [9, 10]  **OUTCOMES:**  **1. Pain assessment**  Mean 0-10 NRS of the day till Day 7 (Pandey studies) [7, 8]  Number of patients with VRS > 1 at rest (0-4 VRS) till 16-hrs after extubation; then at 1 and 3 months at rest and during movement = to assess chronic pain (Pesonen study)  VAS (0-10), at rest and at deep breath till H48; then at 1 and 3 months at rest and during movement = to assess chronic pain (Joshi study)  **Forrest plot for NRS (0-10)** = -3 [-4 to -3] (Pandey studies) [7, 8]  NB: NRS is also significantly reduced in the gabapentin group compared to carbamazepine group in Pandey 2005.  Pesonen study:  **Proportion of patient with VRS>1 at H16 postextubation:** RR 0.3 (0.1 to 0.8)  **Proportion of patient with VRS>1 at 1 and 3 months: NS except at 3 months during movement:**  RR 0.14 (0.02 to 1.04) but crosses the line...  Joshi study:  **VAS only provided as a figure, not computed**  **Breakthrough pain in first 48hrs (average #/pt)** : MD 1.45 lower (2.13 lower to 0.77 lower  **2. Opioid consumption in first 24 hours (morphine equivalent): 4 RCTs**  (Fentanyl in Pandey [7, 8] studies, oxycodone in Pesonen [9], tramadol in Joshi [10])  MD 13.54 lower (14.57 lower to 12.5 lower)  **3. Time to extubation (hours): 2 RCTs in patients after elective cardiac surgery** (Pesonen [9], Joshi [10])  MD 0.36 higher (0.7 lower to 1.43 higher) -> NS  **4. ICU LOS (days): 2 RCTs in patients after elective cardiac surgery** (Pesonen [9], Joshi [10])  MD 0.04 lower (0.46 lower to 0.38 higher) -> NS  **Other outcomes:**  **1) Sedation level:**  Pesonen [9]:  RASS was significantly lower (**more** sedated) only at H2 post extubation in the pregabalin group, but not at H0, H4, 6, 8, 10, 12, 16.  RASS was not significantly different in Joshi [10]  Pandey 2002 [7]  Ramsay was significanlty lower (**less** sedated) in gabapentin group at Day 1 to Day 7  Pandey 2005 [8]:  idem for gabapentin vs carbamazepine and placebo, as well as for CBZ versus placebo  **2) Delirium:** CAM-ICU *"score"* higher in the pregabalin group (24 vs 21, p=0.04) meaning that delirium was reduced in the pregabalin group: only at Day1, not at Day2 to 5, MMSE at Day5 = NS  **3) Nausea** NS (Pesonen, Joshi)[9, 10], **diarrhea constipation** NS (Pandey 2005)[8]  **4) Heart rate, mean arterial pressure, respiratory depression** NS (Joshi)[10]  **Peak inspiratory flow rates** (incentive spirometry) were higher in pregabalin group as compared to control group at 12, 24 and 36 h from extubation (P < 0.05) (Joshi)[10] |  |
| Desirable Effects | **How substantial are the desirable anticipated effects?**  ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know |  | **"large"**because there is an important reduction in pain intensity as well as a reduction in opioid consumption  - Moderate or Large |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**  ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | **"trivial" - some undesirable effects not reported (e.g., dizziness)**  **Bram: consider gap in the literature and those reported in selected studies**  **Group agrees to "small"** |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**  ○ Very low ○ Low ● Moderate ○ High ○ No included studies | Pandey [7, 8] studies seem to have a low ROB but exclusion of patients after enrollment was not reported. Also, these two studies came from the same single center in India: Indian patients might have different pharmacoK/D than other populations? Any Pharm recommendation John?  Pesonen study [9]: very high ROB: 10 on 70 patients were excluded, no intent to treat analysis  Note that the population's size of each group in these 3 RCTs varies from n=12 to n=31 only. | **"moderate" certainty of the evidence of effects**  because 4 double blinded RCTs but with limitations  -it should be whatever the harm of using the drug is - moderate is fair |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**  ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes | Neuropathic pain is difficult to treat with opioids. | **"No important" uncertainty**  to be consistent with previous questions |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know |  | **"Favors" the intervention**  because there was a strong reduction in pain intensity, as well as a strong reduction in opioid consumption, a significant improvement in vigilance status and some improvement in CAM-ICU in one study (at Day 1 only).  No other side effects when assessed, especially nausea, diarrhea, constipation. |
| Resources required | **How large are the resource requirements (costs)?**  ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know | Costs of neuropathic agents are small in France. What in US and Canada?  Low costs and accessible. | **Negligible costs and savings** |
| Certainty of evidence of required resources | **What is the certainty of the evidence of resource requirements (costs)?**  ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies |  | **No included studies**  (no cost-effectiveness study, to be consistent with other questions) |
| Equity | **What would be the impact on health equity?**  ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Feasibility | **Is the intervention feasible to implement?**  ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know | Neuropathic agents require the use of a gastric tube in patients unable to swallow, as well as the absence of ileus. | **"varies"**  **Yes or Probably yes when not focusing on specific ICU patients with CI**  **Probably yes** |

**Summary of judgements**

|  | **Judgement** | | | | | | | **Implications** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |  |
| **Desirable Effects** | Trivial | Small | Moderate | **Large** |  | Varies | Don't know |  |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |  |
| **Certainty of evidence** | Very low | Low | **Moderate** | High |  |  | No included studies |  |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  | No known undesirable outcomes |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | **Favors the intervention** | Varies | Don't know |  |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |  |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |  |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |  |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |  |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |  |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |  |

**Should adjunct neuropathic agent vs. no adjunct neuropathic drug be used for ICU pain management (5.2)?**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ○ | ○ | ○ | ● | |
| **Recommendation** | 1. We recommend to use adjunctive gabapentin to treat neuropathic pain and reduce opioid consumption in ICU patients with Guillain-Barré syndrome (+1B).  2.1. We suggest that adjunctive neuropathic agents be used to treat neuropathic pain in ICU patients, i.e. patients with neuropathic pain related to ICU-aquired weakness (+2B).  2.2. We suggest that adjunctive pregabalin might be used to decrease postoperative pain intensity and opioid consumption in some patients (+2B).  have 2 recommendations: we recommend using neuropathic agents to treat neuropathic pain in the ICU (strong recommendation); weak recommendation for postoperative pain in CV surgery |
| **Justification** | Four RCTs. Two in patients with Guillain-Barré syndrome, low ROB but from a single center and small size population; Two in patients after selective cardiac surgery, two centers, small size population, high ROB for one study.  -> These RCTs are downgraded to a level of evidence of B  Also see recent metaanalyses:  **Pharmacological treatment for pain in Guillain-Barré syndrome.** Jia Liu, Lu-Ning Wang, Ewan D McNicol. ***The Cochrane Library 2013 [11]***  *Although reductions in pain severity were found when comparing gabapentin and carbamazepine with placebo, the evidence was limited and its quality very low. Larger, well-designed RCTs are required to further investigate the efficacy and safety of potential interventions for patients with pain in GBS. Additionally, interventions for pain in the convalescent phase of GBS should be investigated.*  **Perioperative use of pregabalin for acute pain—a systematic review and meta-analysis.** Naveen Eipea, John Penninga, Fatemeh Yazdib, Ranjeeta Mallickb, Lucy Turnerb, Nadera Ahmadzaib, Mohammed Toseef Ansarib. ***PAIN 2015 [12]***  *Pregabalin analgesic effectiveness is largely restricted to surgical procedures associated with pronociceptive mechanisms. The clinical significance of observed pregabalin benefits must be weighed against the uncertainties about serious harms and enhanced recovery to inform the careful selection of surgical patients.* |
| **Subgroup considerations** | There is no data regarding pain in patients with ICUAW. However, there is an empirical evidence that these patients can suffer from typical neuropathic pain. Pathophysiological mechanism in ICUAW is likely similar to patients with Guillain-Barré syndrome. Further studies are needed to investigate pain in ICU patients with ICUAW, as well as the effect of adjunctive neuropathic agents to prevent and treat pain, and reduce opioid consumption. |
| **Research priorities** | This is top priority to investigate analgesics that can decrease the use or dose of opioids to treat pain in ICU patients as well as to investigate analgesics effective to treat neuropathic pain specifically.  These results require that these studies be replicated:  - in medical or surgical patients having neuropathic pain related to ICUAW  - non communicant patients, i.e. at the early stage of sedation-analgesia |
| **comments during electronic Voting by Entire panel** | Can’t generalize GBS patient data to all critically ill patients. |

**Question**: Adjunctive lidocaine compared to no lidocaine for ICU analgesic regime (5.2)

**Setting**: Intensive Care Unit

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Adjunctive lidocaine** | **no lidocaine** | **Relative (95% CI)** | **Absolute (95% CI)** |
| VAS Score at 96 hours (follow up: mean 96 hours; assessed with: VAS; Scale from: 0 to 10) | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | not serious b | serious c | none | 44 | 45 | - | MD **0.1 cm higher** (0.38 lower to 0.58 higher) | ⨁⨁◯◯ LOW | IMPORTANT |
| Total postoperative fentanyl required (assessed with: dosage (mcg)) | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | not serious b | serious c | none | 44 | 45 | - | MD **68.73 mcg lower** (387.372 lower to 249.912 higher) | ⨁⨁◯◯ LOW | IMPORTANT |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. unclear method of randomization, no intention to treat, exclusion of patients unclear

b. Only included cardiac ICU patients; however effects may be generalizable

c. Wide confidence intervals cannot distinguish if clinically important benefits with lidocaine adjunct

|  |  |  |  |
| --- | --- | --- | --- |
| **Question** | | | |
| Should **Adjunctive lidocaine** vs. **no lidocaine** be used for **ICU analgesic regime (5.2)**? | | | |
| **Population:** | ICU analgesic regime (5.2) | **Background:** |  |
| **Intervention:** | Adjunctive lidocaine |
| **Comparison:** | no lidocaine |
| **Main outcomes:** | VAS Score at 96 hours; Total postoperative fentanyl required; |
| **Setting:** | Intensive Care Unit |
| **Perspective:** |  |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | It is top priority to investigate the effectiveness/side effects of Adjunct Non opioid analgesics to opioids compared to opioids alone in order to decrease opioids related side effects that are especially at risk in ICU patients:  - respiratory depression  - neurological impairment (decreased vigilance, delirium)  - ileus, nausea vomiting, etc...  One single center double-blinded RCT in 100 postcardiac surgery ICU patients, high ROB (No flow chart, exclusion of patients unclear, one patient in the intervention group was excluded from analysis because of death, no intent to treat analysis) **-> Insler 1995 [13]**  NB: lidocaïne or placebo was begun just after induction of anesthesia  Pain intensity at H96 (VAS in cm): MD 0.1 higher (0.4 lower to 0.6 higher)  Fentanyl consumption (µg): MD 68 lower (39 lower to 249 higher)  Ramsay score: Lidocaïne group significantly more sedated (higher score) at H4, not at H1, 2, 8, 16, 24, 48, 96.  Other outcomes NS: hemodynamics, midazolam, propofol dosages, time to extubation, ICU LOS, hospital LOS |  |
| Desirable Effects | **How substantial are the desirable anticipated effects?**  ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know |  | **"trivial"** because there was globally no (significant) effect at all.  Also crossed the line of no effect. |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**  ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know | **"trivial"**  because there was globally no (significant) effect at all. |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**  ○ Very low ● Low ○ Moderate ○ High ○ No included studies | Only one study, high ROB: ,o flow chart, exclusion of patients unclear, one patient in the intervention group was excluded from analysis because of death, no intent to treat analysis | **"low"** |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**  ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes |  | **"Possibly important uncertainty or variability"**because except fo hemodynamics (HR, MAP, PAP, CVP, CO, CI and monitoring for myocardial infarction by ECG and CPK enzymes), lidocaïne's related toxicity was not reported: arrhythmias, Central Nervous System (CNS) toxicity (seizures...)   * No uncertainty about VAS |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  | **"Does not favor either the intervention or the comparison"** |
| Resources required | **How large are the resource requirements (costs)?**  ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know | Lidocaïne costs are small. | **"Negligible costs and savings"** |
| Certainty of evidence of required resources | **What is the certainty of the evidence of resource requirements (costs)?**  ○ Very low ○ Low ○ Moderate ● High ○ No included studies |  | Old drug, not expensive and available  -impact of nursing for cardiovascular assessment –  recent meta-analyses available |
| Cost effectiveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**  ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies | No intervention | **"Favors the comparison"**because adjunctive lidocaïne seems to be futile; not using IV lidocaïne saves the (small) cost of the drug but also the administration materials, as well as pharm and nurses' time.  -Probably favors (only one study) |
| Equity | **What would be the impact on health equity?**  ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know |  | **"no"**because adjunctive lidocaïne seems to be futile; not using IV lidocaïne saves the (small) cost of the drug but also the administration materials, as well as pharm and nurses' time.  Probably no to be consistent with previous question |
| Feasibility | **Is the intervention feasible to implement?**  ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  | Take into account required monitoring |

**Summary of judgements**

|  | **Judgement** | | | | | | | **Implications** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |  |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |  |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |  |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |  |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  | No known undesirable outcomes |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |  |
| **Resources required** | Large costs | Moderate costs | **Negligible costs and savings** | Moderate savings | Large savings | Varies | Don't know |  |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | **High** |  |  | No included studies |  |
| **Cost effectiveness** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | No included studies |  |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |  |
| **Acceptability** | No | **Probably no** | Probably yes | Yes |  | Varies | Don't know |  |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |  |

**Should Adjunctive lidocaine vs. no lidocaine be used for ICU analgesic regime (5.2)?**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ● | ○ | ○ | ○ | |
| **Recommendation** | We suggest against using adjunctive IV lidocaïne systematically in addition to opioids to treat pain and/or to reduce opioid consumption in postoperative ICU patients (-2C).  Note: a weak recommendation does not imply that it cannot be used |
| **Justification** | Only one low quality negative RCT in postcardiac ICU patients that investigated pain.  -> level of evidence is downgraded to C  Also to take into consideration the recent Cochrane review (**Continuous intravenous perioperative lidocaine infusion fo postoperative pain and recovery, by Kranke et al. Cochrane Library 2015**)[14], Authors’ conclusions:  There is low to moderate evidence that this intervention, when compared to placebo, has an impact on pain scores, especially in the early postoperative phase, and on postoperative nausea. There is limited evidence that this has further impact on other relevant clinical outcomes, such as gastrointestinal recovery, length of hospital stay, and opioid requirements. So far there is a scarcity of studies that have systematically assessed the incidence of adverse effects; the optimal dose; timing (including the duration of the administration); and the effects when compared with epidural anaesthesia. |
| **Subgroup considerations** | Cardiac surgery patients |
| **Implementation considerations** |  |
| **Monitoring and evaluation** | Lidocaïne's heart and Central Nervous System (CNS) toxicity needs to be investigate in critically ill patients. |
| **Research priorities** | This is top priority to investigate analgesics that can decrease the use or dose of opioids to treat pain in ICU patients.  There is only one negative study in postoperative ICU patients. A Cochrane review reported low to moderate evidence that IV lidocaïne reduced pain at the early stage of postoperative period, opioid consumption as well as improved bowel function, especially after abdominal surgery Future studies are required:  - in SICU patients recovering from an abdominal surgery  - in medical ICU, especially non communicant patients at the early stage of sedation-analgesia |
| **comments during electronic Voting by Entire panel** | specific contexts could be clinically useful: neuro-muscular and neuro patients (post-op or in general), recovering opiate addicts?  "We do not suggest routine lidocaine" harmonizes with the Cochrane review’s modest benefit& this keeps the door open to considering its use. Surprising contrast between this and the ketamine recommendation (where there seemed to be as little data yet a recommendation) |

**Question**: Adjunct NSAIDs compared to no adjunct NSAIDs for postoperative ICU patients (5.2)

**Setting**:

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **adjunct NSAIDs** | **no adjunct NSAIDs** | **Relative (95% CI)** | **Absolute (95% CI)** |
| VAS Pain Score 24 hours postoperatively | | | | | | | | | | | | |
| 2 | randomised trials | serious a | not serious | not serious | serious b | none | 104 | 53 | - | MD **0.35 lower** (0.91 lower to 0.21 higher) | ⨁⨁◯◯ LOW | CRITICAL |
| Opioid Consumption (morphine equivalents) | | | | | | | | | | | | |
| 2 | randomised trials | serious a | serious c | not serious | serious d | none | 49 | 53 | - | MD **1.61 lower** (2.42 lower to 0.8 lower) | ⨁◯◯◯ VERY LOW | CRITICAL |
| VAS Pain Score with Deep Breath at 6 hours | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | serious d | none | 21 | 22 | - | MD **1.3 lower** (2.36 lower to 0.24 lower) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| VAS Pain Score with Deep Breath at 24 hours | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious d,e | none | 21 | 22 | - | MD **0.6 lower** (1.44 lower to 0.24 higher) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. No intention to treat in either analysis, unclear method of randomization

b. Unclear if benefit with adjunctive NSAIDs based on meta-analysis

c. Very high degree of inconsistency (Isquared = 92%) with non overlapping confidence intervals however both show benefit so lowered one level

d. Small sample size

e. Confidence Intervals include both harm and benefit

|  |  |  |  |
| --- | --- | --- | --- |
| **Question** | | | |
| Should **adjunct NSAIDs** vs. **no adjunct NSAIDs** be used for **postoperative ICU patients (5.2)**? | | | |
| **Population:** | postoperative ICU patients (5.2) | **Background:** |  |
| **Intervention:** | adjunct NSAIDs |
| **Comparison:** | no adjunct NSAIDs |
| **Main outcomes:** | VAS Pain Score 24 hours postoperatively; Opioid Consumption (morphine equivalents); VAS Pain Score with Deep Breath at 6 hours; VAS Pain Score with Deep Breath at 24 hours; |
| **Setting:** |  |
| **Perspective:** |  |

**Assessment**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Judgement** | **Research evidence** | **Additional considerations** |
| Problem | **Is the problem a priority?**  ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know | It is top priority to investigate the effectiveness/side effects of Adjunctive Non opioid analgesics to opioids compared to opioids alone in order to decrease opioids related side effects that are especially at risk in ICU patients:  - respiratory depression  - neurological impairment (decreased vigilance, delirium)  - ileus, nausea vomiting, etc... Two single center RCT in ICU patients after surgery  Small size of every group in both studies: from 21 to 31 patients  High ROB for both studies: no intention to treat, unclear method of randomization  **- Hynninen 2000 :** elective cardiac surgery, n=120 (4 groups: 3 different NSAIDs and placebo)  **- Oberhofer 2005 [15]:** abdominal surgery, n=43 (2 groups: ketopropfen and placebo)  **Pain measurement:**  VAS 0-10 in Hyminnen at H3, 6, 12, 24 (at rest only)  NRS 0-10 in Oberhoffer [15] at H3, 6, 12, 24 (at rest and deep breath) | **Drugs:**  **Hynninen:**  Adjunctive 75 mg diclofenac or 100 mg ketoprofen or 100 mg indomethacin or placebo (4 groups) one hour before intubation (*note: how is it possible to know the extubation time exactly!?!*) and 12 hours afterward  Basal analgesia: none?  Rescue analgesia: morphine in the ICU (and mepiridine for shivering); paracetamol, codeine in the ward (transfer on Day 1)  **Oberhofer:**  Adjunctive 100 mg ketoprofen IV one and nine hours postop  Basal analgesia: tramadol and metamizole  Rescue analgesia: tramadol 25 mg IV |
| Desirable Effects | **How substantial are the desirable anticipated effects?**  ○ Trivial ● Small ○ Moderate ○ Large  ○ Varies ○ Don't know | **Forest plot for pain scales (0-10)** **at rest**: MD 0.35 fewer (0.91fewer to 0.21 more)  NB: data are provided only in a figure of means without SD for Hynninen, not estimable for the forrest plot ; in the body text: non significant difference at all times.  Pain at deep breath (Oberhofer) [15]:  H6: MD 1.3 fewer (2.36 fewer to 0.24 fewer)  H 24: MD 0.6 fewer (1.44 fewer to 0.24 more)  **Forest plot for morphine consumption at H24 (mg equivallent)**:  MD 1.61 fewer (2.42 fewer to 0.8 fewer)  **Other outcomes:**  - Nausea and/or vomiting: non significant difference in NSAIDs groups versus placebo (both studies) but very small size groups, probable lack of power  - Other opioid related effects not reported, including: sedation, ileus, duration of MV, LOS in ICU... only "respiratory depression" was reported in Oberhofer [15]: no case in any group  - Serum creatinine: non significant change between groups but one patient had an important increase in S-creatinine after the first dose of indomethacine and was withdrawn of Hynninen's study (no intent to treat analysis!)  - No significant difference in excessive bleeding but again, a probable lack of power, also note that one patient in the indomethacin group had excessive bleeding and was withdrawn of Hynninen's study (no intent to treat analysis!)  - No platelet anti-agregant test was performed to show any effect on platelet function  - Incidence of peptic ulcer in the postoperative period was not reported | **"small" desirable anticipated effects**  because non significant reduction in pain intensity at rest H24, a significant reduction at deep breath in one study, a very small reduction in opioid consumption at H24 |
| Undesirable Effects | **How substantial are the undesirable anticipated effects?**  ○ Large ○ Moderate ○ Small ○ Trivial  ○ Varies ● Don't know | **don't know" undesirable anticipated effects**  because non significant difference for adverse outcomes but two severe adverse events possibly related to NSAID among 30 patients who received indomethacin, no intent to treat analysis; no platelet functional test used on bothe studies |
| Certainty of evidence | **What is the overall certainty of the evidence of effects?**  ○ Very low ● Low ○ Moderate ○ High ○ No included studies | Small size of every group in both studies: from 21 to 31 patients  High ROB for both studies: no intention to treat, unclear method of randomization  - Hynninen: 6 patients were excluded among 120, included two for indometacine possible side effect  - Oberhofer [15]: no patient seems to be excluded after enrollement in the intervention group, one for rash in the control group | **"low" certainty of the evidence of the effects** |
| Values | **Is there important uncertainty about or variability in how much people value the main outcomes?**  ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability ○ No known undesirable outcomes |  | **"no important" uncertainty about or variability in how much people value the main outcomes** to be consistent with previous questions |
| Balance of effects | **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know |  | **"don't know" if the balance between desirable and undesirable effects favor the intervention or the comparison**  because of no or small benefits (no reduction in pain intensity at rest at H24, very small reduction in opioid consumption within 24h) and don't know harms |
| Resources required | **How large are the resource requirements (costs)?**  ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know | NSAIDs costs are small. | **"don't know" about the resource requirements** because severe adverse events related to drugs can be very expensive. See assessment of undesirable effetcs. |
| Certainty of evidence of required resources | **What is the certainty of the evidence of resource requirements (costs)?**  ○ Very low ● Low ○ Moderate ○ High ○ No included studies |  | **"low" certainty of the evidence of ressource requirements**  See assessment of undesirable effetcs. |
| Cost effectiveness | **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**  ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies |  | **No included studies** because no cost-effectiveness study, potential unassessed harms. |
| Equity | **What would be the impact on health equity?**  ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability | **Is the intervention acceptable to key stakeholders?**  ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know |  | **intervention acceptable to stakeholders -> "probably NO"**  because no or small benefits and potential harms related to the intervention. |
| Feasibility | **Is the intervention feasible to implement?**  ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know |  |  |

**Summary of judgements**

|  | **Judgement** | | | | | | | **Implications** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |  |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |  |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | Varies | **Don't know** |  |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |  |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | Probably no important uncertainty or variability | **No important uncertainty or variability** |  |  | No known undesirable outcomes |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **Don't know** |  |
| **Resources required** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |  |
| **Certainty of evidence of required resources** | Very low | **Low** | Moderate | High |  |  | No included studies |  |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |  |
| **Equity** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |  |
| **Acceptability** | No | **Probably no** | Probably yes | Yes |  | Varies | Don't know |  |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |  |

**Conclusions**

**Should adjunct NSAIDs vs. no adjunct NSAIDs be used for postoperative ICU patients (5.2)?**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of recommendation** | |  |  |  |  |  | | --- | --- | --- | --- | --- | | Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention | | ○ | ● | ○ | ○ | ○ | |
| **Recommendation** | We suggest against using adjunctive NSAIDs to prevent pain in ICU patients (-2C). |
| **Justification** | **Overall justification**  Two RCTs but single centers, high ROB, small size  -> level of evidence downgraded to C  **Detailed justification**  *Problem* Surgical ICU population (one cardiac, one abdominal). However, generalization of the results to another kind of population is likely because pain is frequent in SICU patients as in medical ICU patients.  *Desirable Effects* No or small desirable effects  *Undesirable Effects* Some severe adverse events possibly related to NSAID reported in one study, no intent to treat analysis, small size studies that cannot conclude about these adverse events |
| **Subgroup considerations** |  |
| **Implementation considerations** |  |
| **Monitoring and evaluation** | Analgesic related side effects or outcomes should be assessed more largely including:  -delirium  -ileus  -duration of MV weaning  -LOS in ICU and hospital NSAIDs related side effects should be assessed more precisely:  - postoperative bleeding should be defined according to standardized definitions  - risk of bleeding should be assessed by anti-agregant platelet tests, instead of activated coagulation time  - peptic ulcer |
| **Research priorities** | This is top priority to investigate analgesics that can decrease the use or dose of opioids to treat pain in ICU patients.  This kind of study needs to be replicated: - in medical ICU- non verbal patients |
| **comments during electronic Voting by Entire panel** | Single RCT; 1-2 doses likely safe/ effective, more may shift the benefit/burden ratio  add "non-procedural pain" as we for procedural pain. |

**Question**: Cybertherapy compared to no cybertherapy for ICU pain management (5.3)

**Setting**: Non-pharmacological analgesic therapies

**Bibliography**:

| **Quality assessment** | | | | | | | **Impact** | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| # of patients with reduced pain post-cybertherapy | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | serious a | none | Mosso-Vazques [16] used virtual reality cybertherapy to reduce postoperative pain in cardiac surgical ICU patients. 67 patients were monitored within the first day postoperatively. Pain scores were obtained pre- and post-cybertherapy. 59/67 patients (88%) reported a decreased level of pain, with a mean Likert scale change of 3.75, corresponding with a change from severe to moderate, or moderate to light. Physiologically, 25 (37.3%) patients experienced reduced heart rates, 35 (52.2%) experienced reduced MAPs, and 14/22 (64% tested for respiratory rates experienced a reduction. | ⨁◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval

#### Explanations

a. Small sample size

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Question: Should cybertherapy vs. no cybertherapy be used for ICU pain management (5.3)? | | | | | |  |
| Population: | | ICU pain management | | Background: |  |
| Intervention: | | cybertherapy | |  |
| Comparison: | | no cybertherapy | |  |
| Main outcomes: | | # of patients with reduced pain post-cybertherapy | |  |
| Setting: | | Non-pharmacological analgesic therapies | |  |
| Perspective: | |  | |  |
| **Assessment** | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | **Additional considerations** | |
| Problem | **Is there a problem priority?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  | Non-pharmacological interventions for pain management are important in the ICU and could contribute to reduce pain and to improve pain control in patients. | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ● Very low  ○ Low  ○ Moderate  ○ High | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | # of patients with reduced pain post-cybertherapy | CRITICAL | ⨁◯◯◯ VERY LOW | | **Summary of evidence:**  Only 1 observational study (pre/post) was included (Mosso-Vazquez et al., 2014) [16].  The aim was to evaluate the use of virtual reality (VR) cybertherapy on postoperative distress in cardiac surgery ICU patients. 67 patients navigated a 30-minute VR simulation designed for pain management.  59 patients (88%) reported a decreased level of pain post-therapy. The mean change was 3.75 on a Likert scale (unsure what the possible range was). The authors described that change as a decrease from severe to moderate or moderate to liht. Methods section very brief and poorly written.  **Uncertainty about main outcomes:**  -unsure what the Likert scale scores are.  -important uncertainty or variability  -important uncertainty or possibly important  **Are the desirable anticipated effects large?**  I put uncertain because we only have 1 observational study, the sample size was small and the method is questionable. On the other hand, a change in 3.75 would be considered clinically significant if we would know what the scores mean (Likert scale).  Group: uncertain - we don't really know  **Are the undesirable anticipated effects small?**  Complications (6% of patients) during treatment included cardiac arrhythmia (n=1), and nausea and vertigo (n=3) that interrupted cybertherapy session (p.375). Based on this information, I am hesitant between Probably no and Uncertain.  - these complications could happen anytime  -happen frequently in cardiac ICU patients  -uncertain because could happen during the intervention too; number is too small to make a judgment  Consensus from the group for uncertain  **Are the desirable effects large relative to undesirable effects?**  Uncertain because unsure about the desirable effects and complications were reported (but in a small number of patients).  Consensus from the group for uncertain | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ● Important uncertainty or variability  ○ Possibly important uncertainty or variability  ○ Probably no important uncertainty or variability  ○ No important uncertainty or variability  ○ No known undesirable outcomes |
| **Are the desirable anticipated effects large?** | | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies |
| **Are the undesirable anticipated effects small?** | | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies |
| Resource use | **Are the resources required small?** | | ○ No  ● Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ○ Varies | A head-mounted display was installed on the patient's head to display a VR simulation. A projector emitted the same simulation on the unit wall. The simulation consisted of five cybertherapy environments. The simulation lasted 30 minutes. | Special equipment is necessary for this intervention and time and resources to develop the simulations should also be taken into account.  - addresses music therapy as an example and all the necessary resources needed  - No - enormous amount of resources`probably no also acceptable  -Probably no  - Probably no  Pt: Probably no | |
| **Is the incremental cost small relative to the net benefits?** | | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies |  | RCTs are necessary to confirm conclusions on the effectiveness of this intervention on pain management.  Costs for this intervention should be considered.  We cannot conclude that benefits exceeded the costs.  Consensus from the group for uncertain. | |
| Equity | **What would be the impact on health inequities?** | | ○ Increased  ○ Probably increased  ○ Uncertain  ○ Probably reduced  ○ Reduced  ○ Varies |  |  | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies |  | The ICU environment and access to equipment and resources will likely influence the acceptability of this intervention by stakeholders.  Consensus from the group for uncertain | |
| Feasibility | **Is the option feasible to implement?** | | ○ No  ● Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ○ Varies |  | Many factors (equipment, time, resources, ICU environment, training) should be taken into account.  Consensus for probably no | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Recommendation**  **Should cybertherapy vs. no cybertherapy be used for ICU pain management (5.3)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation** | We recommend against offering VR cybertherapy until further research is available.  From Bram: I agree with your assessments. You may consider recommending more research and in the meantime recommending against (conditionally) until more research is available. Alternatively you could just recommend further work without making a formal recommendation. My slight preference would be for the former. | | | |
| **Justification** | I believe because of the very low evidence and the complications reported, the balance of desirable and undesirable consequences is uncertain. But maybe the reduction in pain level probably outweigh the risks.  I would be in favor of suggesting to conduct RCTs to allow a higher level of evidence to conclude on the effectiveness of such an intervention. | | | |
| **Subgroup considerations** | Only 1 observational study conducted with cardiac surgery ICU patients. Small sample size. No inferential statistics. | | | |
| **Implementation considerations** | Many factors to be taken into account including the ICU environment, access to technology, resources. and training | | | |
| **Monitoring and evaluation** | We need RCTs to draw firm conclusions about the effectiveness of such an intervention. | | | |
| **Research possibilities** | Rationale for recommendation: There is a major gap in research (1 observational study). Measure issue for pain (Likert scale). Small sample size (no power analysis) and inferential statistics not used.  Other virtual interventions could be developed and tested. The use of touchpad or tablet could be considered. | | | |

**Question**: Hypnosis + pharmacological therapies compared to no hypnosis for critically ill pain management patients (5.4)

**Setting**:

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Hypnosis + pharmacological therapies** | **no hypnosis** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Daily VAS Score (cm) | | | | | | | | | | | | |
| 1 | observational studies | very serious a | not serious | not serious | very serious b,c | none | 23 | 23 | - | MD **0.5 lower** (1.37 lower to 0.37 higher) | ⨁◯◯◯ VERY LOW | CRITICAL |
| Morphine Equivalents | | | | | | | | | | | | |
| 1 | observational studies | very serious a | not serious | not serious | very serious b | none | Pre-post morphine equivalent dosing was not provided for the control arm. Intervention arm did have a large decrease in morphine equivalents between days 10-15; the authors attribute this to the completion of surgeries and wound management in these burn patients. | | | | ⨁◯◯◯ VERY LOW | CRITICAL |
| Propofol Requirements (mg) | | | | | | | | | | | | |
| 1 | observational studies | very serious a | not serious | not serious | very serious b | none | 23 | 23 | - | MD **380 mg lower** (523 lower to 237 lower) | ⨁◯◯◯ VERY LOW | IMPORTANT |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. Inaccurate assessment of outcomes, variability on co-interventions between groups, unclear ascertainment of exposure

b. Small sample size (only 23 patients eligible)

c. CI cross line of no effect

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Question** Should Hypnosis + pharmacological therapies vs. no hypnosis be used for critically ill pain management patients (5.4)? | | | | | |  |
| Population: | | critically ill pain management patients (5.4) | | Background: |  |
| Intervention: | | Hypnosis + pharmacological therapies | |  |
| Comparison: | | no hypnosis | |  |
| Main outcomes: | | * Daily VAS Score (cm) * Morphine Equivalents * Propofol Requirements (mg) | |  |
| **Assessment** | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | **Additional considerations** | |
| Problem | **Is there a problem priority?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  | Non-pharmacological interventions are important to consider in ICU pain management. | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ● Very low  ○ Low  ○ Moderate  ○ High | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | |  |  |  | | Daily VAS Score (cm) | CRITICAL | ⨁◯◯◯ VERY LOW | | Morphine Equivalents | CRITICAL | ⨁◯◯◯ VERY LOW | | Propofol Requirements (mg) | IMPORTANT | ⨁◯◯◯ VERY LOW | | Only one small observational study (with matched controls, n=23 in each group); many limitations.  **Are the desirable anticipated effects large?**  Pain score MD very small (0.5 lower)  and CI cross line of no effect.  **Are the undesirable anticipated effects small?**  Uncertain; adverse events not reported.  No difference in vital signs (HR, BP, RR), and first bowel movement between groups.  **Are the desirable effects large relative to undesirable effects?**  Probably no, but could put uncertain. We cannot conclude to small desirable effect considering that small observational study, and undesirable effects remain unknown (but unlikely). | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ○ Important uncertainty or variability  ○ Possibly important uncertainty or variability  ○ Probably no important uncertainty or variability  ● No important uncertainty or variability  ○ No known undesirable outcomes |
| **Are the desirable anticipated effects large?** | | ○ No  ● Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ○ Varies |
| **Are the undesirable anticipated effects small?** | | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies |
| Resource use | **Are the resources required small?** | | ○ No  ● Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ○ Varies | In this study, hypnosis was administered by ICU nurses who had completed 3 years of training under the supervision of a psychiatrist. |  | |
| **Is the incremental cost small relative to the net benefits?** | | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies |  | Training appears extensive.  Intervention with many stages; duration may vary between patients. | |
| Equity | **What would be the impact on health inequities?** | | ○ Increased  ○ Probably increased  ● Uncertain  ○ Probably reduced  ○ Reduced  ○ Varies |  | Unlikely | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies |  | Uncertain based on required resources. | |
| Feasibility | **Is the option feasible to implement?** | | ○ No  ● Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ○ Varies |  | Feasibility concerns  Will vary between patients (hypnosibility) | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Recommendation**  **Should Hypnosis + pharmacological therapies vs. no hypnosis be used for critically ill pain management patients (5.4)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ● | ○ | ○ |
| **Recommendation** | No recommendation? The group feels more confortable to not make a recommendation and document why we cannot make recommendation.  Methods- I would steer the group towards a conditional/weak recommendation against given the lack of benefit (acknowledging all very low quality evidence) and the costs/resources involved in training.  I believe there is utility in making a recommendation versus not making one. And I think here a weak recommendation against makes sense - if the group agrees. It doesn't mean we're discouraging future research work and we can be clear about that (always everyone's worry in this case). | | | |
| **Justification** | Little evidence to support a recommendation for hypnosis.  In the justification you can obviously elaborate and say that if future evidence shows benefit this balance may change or in select centers with expertise the balance may be different. | | | |
| **Subgroup considerations** | The included study was conducted in a burn ICU during dressing and hydrotherapy. | | | |
| **Implementation considerations** | Not yet to be considered for implementation, need stronger evidence and RCTs. | | | |
| **Monitoring and evaluation** |  | | | |
| **Research possibilities** | Ideas form the group?  Having higher level of evidence, include other ICU patients and during care procedures. Review research in anesthesia (morphine sparing effects, anesthesia) and specific surgical procedures (pediatric and gynecological). | | | |
| **Comments during electronic voting by entire panel** | Hard to imagine virtual reality as good option for a population at such high risk for delirium (or certainly an altered state of consciousness). | | | |

**Question**: A narcotic compared to placebo for critically ill adults undergoing a procedure (2.1)

**Setting**:

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **a narcotic** | **placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain Score | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious a | not serious | serious b | none | 59 | 56 | - | SMD **1.27 SD lower** (2.79 lower to 0.26 higher) | ⨁⨁⨁◯ MODERATE | CRITICAL |

**CI:** Confidence interval; **SMD:** Standardised mean difference

#### Explanations

a. High Isquared (>90%), although both studies show benefit.

b. Confidence intervals don't exclude harm.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Question** Should a narcotic vs. placebo be used for critically ill adults undergoing a procedure (2.1)? | | | | | |  |
| Population: | | critically ill adults undergoing a procedure (2.1) | | Background: |  |
| Intervention: | | a narcotic | |  |
| Comparison: | | placebo | |  |
| Main outcomes: | | * Pain Score | |  |
| **Assessment** | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | **Additional considerations** | |
| Problem | **Is there a problem priority?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  |  | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ○ Very low  ○ Low  ● Moderate  ○ High | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Pain Score | CRITICAL | ⨁⨁⨁◯ MODERATE | | Two studies included.  Robleda et al (2015)[17] : Randomized, double-blind, paralell group, placebo-controlled clinical trial, 2 groups: 1) fentanyl (1 ug/kg for medical patients and 1.5 ug/kg for surgical/trauma patients) (n=39); and 2) control (n=36).  Procedure: turning in mechanically ventilated patients (heterogeneous group)  Pain measure: BPS ( a score >3 reflects pain, and a score >5 indicates significant pain)  Main findings: Pain incidence rate was significantly lower in the fentanyl group (74%) compared to control group (94%) with a relative risk of 0.79; incidence of significant pain was not statistically different between groups (49% versus 64%) with a relative risk of 0.76. Magnitude of pain (AUC): the fentanyl group had a lower magnitude of pain than the control group during turning and 30 minutes after. Adverse events and vital signs also reported.  Casey et al. (2010): Randomized, double-blind clinical trial, 3 groups: 1) remifentanyl 1 ug/kg (n=20), 2) remifentanyl 0.5 ug/kg (n=20), and 3) placebo (n=20). I assume the remifentanyl 0.5 ug/kg was only included in the evidence table (to be confirmed with John C and Bram).  Procedure: CTR in cardiac surgery ICU patients  Pain measure: 10 cm VAS  Main findings: both remifentanyl groups had no increase in pain scores during CTR compared with baseline (median=1 for remifentanyl 5 ug/kg and 0 for remifentanyl 1 ug/kg; the median was 2 for both groups at baseline); the placebo group showed an increase in VAS pain scores during CTR (median=5). Vital signs data (SBP, HR, RR, SpO2) also reported.  Overall SMD was 1.27 lower  **Are the desirable anticipated effects large?**  Probably yes because did not reach clinical significance reduction in pain (2 cm). More difficult to conclude with BPS, but pain incidence (BPS>3) was lower in the fentanyl group by 20%.  Paul, Kathleen and JF: BPS of 3 indicates no pain behaviors were present? Not necessarily... Nurses can administer analgesics if BPS >4 (JF  **Are the undesirable anticipated effects small?**  Probably yes because no serious adverse events (but 4 patients with respiratory depression in the fentanyl group) reported in Robleda study; 19 non-serious events (e.g., transient hypotension, vomiting) with no significant differences between groups. In Casey study, reductions in all vital signs in the remifentanyl 1 ug/kg group, but only for blood pressure and RR in the remifentanyl 0.5 ug/kg group. No differences in vital signs between groups in Robleda study (increases during turning observed in both groups).  - Respiratory depression is a severe adverse event.  -: Varies because dose dependent.  **Are the desirable effects large relative to undesirable effects?**  Probably yes considering the reductions in pain scores in the opioid groups, and given that adverse events were equally balanced between groups (except for respiratory depression).  -: uncertain because too many factors involved; but ok with  pt-s for probably yes  pt-: in the ICU, the team can deal with respiratory depression; benefits outweighs the undesirable effects | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ○ Important uncertainty or variability  ○ Possibly important uncertainty or variability  ○ Probably no important uncertainty or variability  ● No important uncertainty or variability  ○ No known undesirable outcomes |
| **Are the desirable anticipated effects large?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |
| **Are the undesirable anticipated effects small?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ● Varies |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |
| Resource use | **Are the resources required small?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |  | Opioids are part of standard of care. However, remifentanyl is more expensive compared to fentanyl. | |
| **Is the incremental cost small relative to the net benefits?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |  | Probably yes because opioids are easily accessible in the ICU, and are shown to be effective in reducing pain scores during procedures.  Remifentanil more expensive compared to fentanyl. | |
| Equity | **What would be the impact on health inequities?** | | ○ Increased  ○ Probably increased  ○ Uncertain  ○ Probably reduced  ○ Reduced  ○ Varies |  |  | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |  | Probably yes for fentanyl. For remifentanil, it may vary in different countries based on costs and standard practice. | |
| Feasibility | **Is the option feasible to implement?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |  | Probably yes for fentanyl, but uncertain for remifentanil based on my comments above.  -: Probably yes considering the 2 trials together  - feasible and quick to action  Pt-: adverse effects lasting shorter | |

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| **Recommendation**  **Should a narcotic vs. placebo be used for critically ill adults undergoing a procedure (2.1)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ○ | ● | ○ |

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| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation** | We suggest using an opioid prior to a procedure (e.g., CTR, turning) for pain management in ICU patients (+2B). | | | |
| **Justification** | Well designed RCTs showing reductions in pain scores or pain incidence when opioids are administered compared to a placebo. | | | |
| **Subgroup considerations** | CTR in cardiac surgery ICU patients (Casey) [18]; turning in an heterogeneous ICU patient group (Robleda)[17] | | | |
| **Implementation considerations** | Costs and standard practice in different countries; timing of administration prior to the procedure is important to consider (but quick to act); adverse events may occur and should be monitored and treated in a timely manner | | | |
| **Monitoring and evaluation** | Pain assessment prior and during (or right after the procedure) is key for the evaluation of the effectiveness of analgesia; monitoring of adverse events should also be done | | | |
| **Research possibilities** | Other procedures and other opioids should be tested; for turning, it would be relevant to also include the self-report of pain intensity as a primary outcome  Implementation studies are also needed | | | |

**Question**: High dose narcotic compared to low dose narcotic for critically ill adults undergoing a procedure (2.1)

**Setting**:

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **high dose narcotic** | **low dose narcotic** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain Score (assessed with: SMD) | | | | | | | | | | | | |
| 2 | randomised trials | not serious | serious a | not serious | serious b | none | 78 | 79 | - | SMD **0.26 SD lower** (0.94 lower to 0.42 higher) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **SMD:** Standardised mean difference

#### Explanations

a. High Isquared (70%) and non-overlapping confidence intervals.

b. Wide confidence intervals don't exclude harm.

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| **Question** | | | | | | | |  |
| Should high dose narcotic vs. low dose narcotic be used for critically ill adults undergoing a procedure (2.1)? | | | | | | | |
| Population: | | | critically ill adults undergoing a procedure (2.1) | | Background: | |  |
| Intervention: | | | high dose narcotic | |  | |
| Comparison: | | | low dose narcotic | |  | |
| Main outcomes: | | | * Pain Score | |  | |
| **Assessment** | | | | | | | | |
|  | **Criteria** | **Judgements** | | **Research evidence** | | **Additional considerations** | | |
| Problem | **Is there a problem priority?** | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies | |  | | Pharmacological interventions for procedural pain management are important given the documented prevalence of pain associated with many ICU procedures.  **What is the overall certainty of this evidence? Casey** 2010 [18]:  significantly less pain with CTR or turning after remifentanyl 1 mcg/kg remifentanil IV (n=20) vs remifentanyl 0.5 mcg/kg remifentanil IV (n=20).  CTR pain intensity scores per 0-10 VAS:  Remifentanil 1 mcg/kg = median 0 [0-2]  Remifentanil 0.5 mcg/kg = median 1 [0, 2]  **SMD** -0.66 [-1.30, -0.02]  **Ahlers 2012 [19]**: found no difference in pain with CTR with morphine 7.5 mg IV 30 minutes prior to procedure (n-58) vs morphine 2.5 mg IV 30 minutes prior to procedure (n=59).  (Ahlers did not differentiate between those who were turned vs. turned and CTR.)  Procedural pain scores per 0-10 NRS:  Morphine 7.5 mg IV = mean 2.7 + 2.0-3.4  Morphine 2.5 mg IV = mean 2.6 + 2.0-3.2  **SMD** 0.04 [-0.32, 0.40]  **Overall SMD** -0.26 [-0.94, 0.42]  **NS**  So, only 1 small-sample study with significant findings. | | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | ○ No included studies  ○ Very low  ● Low  ○ Moderate  ○ High | | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Pain Score | CRITICAL | ⨁⨁◯◯ LOW | | | **Are the desirable anticipated effects large?**  No  **Are the undesirable anticipated effects small?** Casey [18] had 2/20 patients with 1-3 minutes of apnea after 1 mcg/kg remifentanil IV, requiring bag and mask ventilation 1 minute after drug administration.  **Are the desirable effects large relative to undesirable effects?**Depends on drug dosage, as in Casey [18].  -Probably no considering that desirable effects are absent.  - No (no positive effects) | | |
| **Is there important uncertainty about how much people value the main outcomes?** | ○ Important uncertainty or variability  ○ Possibly important uncertainty or variability  ○ Probably no important uncertainty or variability  ● No important uncertainty or variability  ○ No known undesirable outcomes | |
| **Are the desirable anticipated effects large?** | ● No | |
| **Are the undesirable anticipated effects small?** | ○ No  ○ Probably no  ● Uncertain | |
| **Are the desirable effects large relative to undesirable effects?** | ● No  ○ Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ○ Varies | |
| Resource use | **Are the resources required small?** | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies | |  | | Administration of opioids is standard practice in ICUs. | | |
| **Is the incremental cost small relative to the net benefits?** | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies | |  | | Pain relief from opioid administration is low cost.  =: Uncertain; Remifentanyl more expensive  Group consensus | | |
| Equity | **What would be the impact on health inequities?** | ○ Increased  ○ Probably increased  ○ Uncertain  ○ Probably reduced  ○ Reduced  ○ Varies | |  | |  | | |
| Acceptability | **Is the option acceptable to key stakeholders?** | ○ No  ● Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ○ Varies | |  | | Administration of opioids is standard practice in ICUs.  - Uncertain because administration of opioids prior to a procedure raise many concerns among ICU clinicians.  - Low versus high doses; so probably no (with high doses).  - Probably no | | |
| Feasibility | **Is the option feasible to implement?** | ○ No  ○ Probably no  ● Uncertain  ○ Probably yes  ○ Yes  ○ Varies | |  | | Administration of opioids is standard practice in ICUs.  However, administration of opioids prior to procedures requires ICU clinicians to probably change practice and plan for this.  - Uncertain with only 2 studies and small samples in a homogeneous population.  -Uncertain; will depend on intubation status and communication between nurses and physicians | | |

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| --- | --- | --- | --- | --- | --- |
| **Recommendation Should high dose narcotic vs. low dose narcotic be used for critically ill adults undergoing a procedure (2.1)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

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| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation** | A substantial body of research demonstrates the painfulness of turning and chest tube removal.  Pain should be assessed prior to a procedure, and administration of analgesics to address baseline as well as procedural pain should be made a standard part of practice.  Opioids in low doses should be considered for procedural pain management. (in both studies, the scores were low no matter low or high doses were used)  We suggest using opioids for chest tube removal. If using opioids, we suggest using low doses versus high doses. Little benefit and use of low versus high doses of opioids; I would suggest not offering this option. Recommending lower doses would be a better option. No benefit to administer opioids when pain at baseline is low. No control groups (with no opioids) in these studies For semantics, better to use positive than negative. | | | |
| **Justification** | 2013 PAD Guidelines [20] recommended use of analgesics prior to CTR. | | | |
| **Subgroup considerations** | Ahlers [19] did not differentiate between patients being turned and patients being turned and having CTR.  This confounds study findings.  However, Ahlers said that patients just having CTR had significantly less pain than patients just being turned. | | | |
| **Implementation considerations** | Administration of opioids prior to a procedure should be timed to the analgesic's peak effect, occurring at time of procedure. | | | |
| **Monitoring and evaluation** | Pre and post pain assessments to evaluate impact of the intervention.  Potential adverse effects from opioids should be monitored. | | | |
| **Research possibilities** | Study one procedure e.g., CTR using equianalgesic dose of remifentanyl 0.5 mcg/kg IV in a large sample. Alternative opioids. | | | |
| **Comments during electronic voting by entire panel** | RCT showing fentanyl (1-1.5 mcg/kg/ dose) before turning in mixed, MV population ↓ pain by BPS by 20%, NNT 5 (Robleda ICM 2016); 10% got respiratory depression.  Caveats: Forrest plots (FPs) mitigated by outcomes combined from different studies; #1 improved pain scores opioid vs. placebo, #2 pain score differences with opioids + turning= no difference, also a positive outcome. But combining these different outcomes misleads the FPs. In which pt. population is turning painful**?** | | | |

**Question**: Local analgesia compared to nitrous oxide for critically ill adults undergoing a procedure (2.1)

**Setting**:

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **local analgesia** | **nitrous oxide** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain Score | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | not serious | serious b | none | 22 | 22 | - | MD **27.5 lower** (40.9 lower to 14.1 lower) | ⨁⨁◯◯ LOW | CRITICAL |
| New outcome | | | | | | | | | | | | |
|  |  |  |  |  |  |  |  |  | not estimable |  | - |  |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. No clear description of allocation concealment or blinding in single included study.

b. Confidence intervals don't include no effect however small number of patients.

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| **Question** | | | | | |  |
| Should local analgesia vs. nitrous oxide be used for critically ill adults undergoing a procedure (2.1)? | | | | | |
| Population: | | critically ill adults undergoing a procedure (2.1) | | Background: |  |
| Intervention: | | local analgesia | |  |
| Comparison: | | nitrous oxide | |  |
| Main outcomes: | | * Pain Score | |  |
| **Assessment** | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | **Additional considerations** | |
| Problem | **Is there a problem priority?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  | Pharmacological interventions for procedural pain management are important given the documented prevalence of pain associated with many ICU procedures. | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ○ Very low  ● Low  ○ Moderate  ○ High | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Pain Score | CRITICAL | ⨁⨁◯◯ LOW | | **Are desirable anticipated effects large?**  Only one study:  Akrofi, 2005 [21]. CTR after cardiac surgery.  Either 20 ml of 0.5% bupivacaine SQ infiltration around drain insertion site (comparator) (n=22) or inhaled 50% nitrous oxide and oxygen (Entonox) (control) (n=22). Median pain intensity score 9.5 (3–18) in bupivacaine group vs 37.0 (13–56) in Entonox group (p<0.05).  **SMD**;  - 27.50 [-40.90, -14.10] on 0 - 100 VAS.  Large clinical significance.  No clear description of allocation concealment or blinding in single included study.  **Are the undesirable anticipated effects small?**No difference among groups in arterial blood pressure, heart rate, PaCo2, oxygenation, or sedation.   * : Adverse events less likely to occur with local administration and low doses. Probably yes | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ○ Important uncertainty or variability  ○ Possibly important uncertainty or variability  ○ Probably no important uncertainty or variability  ● No important uncertainty or variability |
| **Are the desirable anticipated effects large?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |
| **Are the undesirable anticipated effects small?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |
| Resource use | **Are the resources required small?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | Re. Entonox use:  While they are a part of intra-operative anesthesia, use of  gas in ICU for procedural pain relief is unusual.  And it was not effective.  Re. bupivacaine use: not a large effort needed to administer subcutaneously around chest tube. | |
| **Is the incremental cost small relative to the net benefits?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | Could be part of standard practice | |
| Equity | **What would be the impact on health inequities?** | | ○ Increased  ○ Probably increased  ○ Uncertain  ○ Probably reduced  ○ Reduced  ○ Varies |  |  | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | A qualified clinician would have to do the subcutaneous infiltration of bupivacaine. | |
| Feasibility | **Is the option feasible to implement?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |  | Medication already available in clinical practice. | |

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| --- | --- | --- | --- | --- | --- |
| **Recommendation**  **Should local analgesia vs. nitrous oxide be used for critically ill adults undergoing a procedure (2.1)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ○ | ● | ○ |

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| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation** | Bupivacaine infiltration is preferred over nitrous oxide prior to CTR. | | | |
| **Justification** | Effective in reducing CTR pain.  Clinically significant pain decrease. | | | |
| **Subgroup considerations** | This study included removal of mediastinal chest tubes in cardiac surgery ICU patients.  The effect on pleural tubes, whose removal is known to be more  painful,  is unknown. | | | |
| **Implementation considerations** | Requires clinician qualified to do infiltration. | | | |
| **Monitoring and evaluation** | Pre- and post- CTR pain scores should be ascertained. | | | |
| **Research possibilities** | Replication of this study with a larger sample with heterogeneous patients and inclusion of a pleural chest tube group.  This study had no clear description of allocation concealment or blinding in single included study.  A future study should address these issues.  Larger sample with enough power to determine differences in adverse effects. | | | |
| **Comments during electronic voting by entire panel** | should an opioid be used instead? Only comparing to opioids? | | | |

**Question**: A narcotic compared to nitrous oxide for critically ill adults undergoing a procedure (2.1)

**Setting**:

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **a narcotic** | **nitrous oxide** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain Score | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | not serious | serious b | none | 22 | 22 | - | MD **22 lower** (36.68 lower to 7.32 lower) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. No clear description of allocation concealment or blinding in single included study.

b. Small number of patients - despite confidence intervals all on side of benefit.

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| --- | --- | --- | --- | --- | --- | --- |
| **Question** | | | | | |  |
| Should a narcotic vs. nitrous oxide be used for critically ill adults undergoing a procedure (2.1)? | | | | | |
| Population: | | critically ill adults undergoing a procedure (2.1) | | Background: |  |
| Intervention: | | a narcotic | |  |
| Comparison: | | nitrous oxide | |  |
| Main outcomes: | | * Pain Score | |  |
| **Assessment** | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | **Additional considerations** | |
| Problem | **Is there a problem priority?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  | Pharmacological interventions for procedural pain management  are important given the documented prevalence of pain associated with many ICU procedures. | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ○ Very low  ● Low  ○ Moderate | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Pain Score | CRITICAL | ⨁⨁◯◯ LOW | | Only one study:  Akrofi, 2005 [21]. CTR after cardiac surgery.  Either 50% nitrous oxide and oxygen (Entonox) (control) 2 minutes before procedure (n=22) or 0.1 mg/kg morphine as an IV bolus over 2 min 20 minutes before procedure (intervention)(n=22.)  Median VAS scores on 0 - 100 scale:  nitrous oxide group: 37.0 [13–56] vs. morphine group: 15.0 [7–27]  **SMD**: -22 [-36.68, -7.32]  Acceptable clinical significance.  No clear description of allocation concealment or blinding in single included study.  **Are anticipated effects large?**  Uncertain or probably no given one study, pain scores not in the moderate-severe levels.  Do we want one of these interventions to have a big difference on pain scores? Nitrous oxide patients had twice more pain than the morphine patients.  Pamela: No differences with 2 and 4/10; side effects not considered.  Gerald: One small study; 37 is pretty high so anticipated effects appear to be large. Could patients with nitrous oxide reliably self-report pain?  -Not considering the sample size and side effects, just looking at this specific question what is the benefit of opioids large? With group: Considering this, probably yes makes sense.  **Are the undesirable anticipated effects small?**No difference among groups in arterial blood pressure, heart rate, PaCo2, oxygenation, or sedation.  **Desirable versus undesirable effects**: Changed to probably yes | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ● No important uncertainty or variability |
| **Are the desirable anticipated effects large?** | | ● Probably yes  ○ Yes  ○ Varies |
| **Are the undesirable anticipated effects small?** | | ● Yes  ○ Varies |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |
| Resource use | **Are the resources required small?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  | Use of IV opioids is part of standard practice. | |
| **Is the incremental cost small relative to the net benefits?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  | No incremental costs. | |
| Equity | **What would be the impact on health inequities?** | | ○ Increased  ○ Probably increased  ○ Uncertain  ○ Probably reduced  ○ Reduced  X○ Varies |  |  | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  | Use of IV opioids is part of standard practice. | |
| Feasibility | **Is the option feasible to implement?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  |  | |

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| --- | --- | --- | --- | --- | --- |
| **Recommendation**  **Should a narcotic vs. nitrous oxide be used for critically ill adults undergoing a procedure (2.1)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ○ | ● | ○ |

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| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation** | We suggest to premedicate patients with opioids instead of nitrous oxide prior to mediastinal chest tube removal. | | | |
| **Justification** | Clinical significance difference in favor of morphine; small study | | | |
| **Subgroup considerations** | This study included removal of mediastinal chest tubes in cardiac surgery patients.  The effect on pleural tubes, whose removal is known to be more  painful,  is unknown.  Use of short-term opioids (e.g., fentanyl, alfentanyl, remifentanyl) to manage short-duration procedures. | | | |
| **Implementation considerations** | Opioids are already implemented in standard practice. | | | |
| **Monitoring and evaluation** | Pain assessment prior to the procedure with validated scales.  Side effect monitoring. | | | |
| **Research possibilities** | Replication of this study with a larger sample and inclusion of a pleural chest tube group.  This study had no clear description of allocation concealment or blinding in single included study.  A future study should address these issues.  Larger sample size necessary to capture adverse events. As a patient, I would prefer nitrous oxide. Differences among different types of opioids in terms of side effects. | | | |

**Question**: Isoflurane & Nitrous Oxide compared to Nitrous oxide alone for critically ill adults undergoing a procedure (2.1)

**Setting**:

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Isoflurane & Nitrous Oxide** | **Nitrous oxide alone** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain Score | | | | | | | | | | | | |
| 1 | randomised trials | serious a | not serious | serious b | serious c | none | Although the Bryden 1997 [22] study showed that Entonox (nitrous oxide plus oxygen) along with isoflurane inhalation was more effective for pain related to the first of 2 chest tubes to be removed, removal of the second tube was more painful, regardless of the gas inhaled. SMD -26.00 [-40.76, -11.24] on a 0 - 100 VAS. | | | | ⨁◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. Unclear description of blinding practices in single included study.

b. Comparator not placebo.

c. Despite confidence intervals that don't cross no effect there was a small number of patients.

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| **Question** | | | | | |  |
| Should Isoflurane & Nitrous Oxide vs. Nitrous oxide alone be used for critically ill adults undergoing a procedure (2.1)? | | | | | |
| Population: | | critically ill adults undergoing a procedure (2.1) | | Background: |  |
| Intervention: | | Isoflurane & Nitrous Oxide | |  |
| Comparison: | | Nitrous oxide alone | |  |
| Main outcomes: | | * Pain Score | |  |
| **Assessment** | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | **Additional considerations** | |
| Problem | **Is there a problem priority?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  | Non-pharmacological interventions for procedural pain management  are important given the documented prevalence of pain associated with many ICU procedures. | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ● Very low | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Pain Score | CRITICAL | ⨁⨁◯◯ LOW | | 35 patients after uncomplicated cardiac surgery; chest tube removal. RCT double-blinded.  Although the Bryden 1997 [22] study showed that Entonox (nitrous oxide plus oxygen) along with isoflurane inhalation was more effective for  pain related to the first of 2 chest tubes to be removed, removal of the second tube was more painful, regardless of the gas inhaled. **SMD** -26.00 [-40.76, -11.24] on a 0 - 100 VAS.  **Are the desirable anticipated effects large?**  Although a SMD difference of 26 points on a 0 - 100 VAS is large, the results differed according to the order of the tube removal.  Change to probably yes considering the change in pain scores and the difference between treatments.  Gerald: Probably no because we should compare the first tube removal - no difference between the 2 groups. Isoflurane given for the first tube, then it stopped. The patient awakened before the second tube removal. It's the effect of NOT having isoflurane for the second tube.  The two tubes should be studied separately. The score difference is due to the study design and not real effects.  **Are the undesirable anticipated effects small?**Patients inhaled gas until drowsy but not unconscious.  Researchers noted no differences between groups in several potential side effects such as nausea, dizziness, smell of gas, but they did not provide statistics on side effects.  **Are the desirable effects large relative to undesirable effects?**Decreased pain scores without reports of side effects.  Probably no | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ● No important uncertainty or variability |
| **Are the desirable anticipated effects large?** | | ○ No  ● Probably no |
| **Are the undesirable anticipated effects small?** | | ○ No  ○ Probably no  ● Uncertain |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ● Probably no |
| Resource use | **Are the resources required small?** | | ● No |  | Gases contained in high pressure cylindars.  While they are a part of intra-operative anesthesia, use of these gases in ICU is unusual.  Researchers noted that the the procedure was supervised by one of them (assume they are anesthesiologists?), the nurses administered the gas.  Study done in Scotland, where nursing practice may differ from other places in the world. | |
| **Is the incremental cost small relative to the net benefits?** | | ● No |  | Although the cost of this intervention was not addressed in the study,  it is assumed that the cost would be large vis a vis the use of a drug analgesic.  (Cost of equipment, cost of physician time.)  More importantly, the effectiveness of this intervention for chest tube removal pain is only based on this one study.  Very expensive; you need monitoring and safety procedures | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ● No |  | For reasons noted above, in incremental costs. | |
| Feasibility | **Is the option feasible to implement?** | | ● No |  | For reasons noted above, in incremental costs. | |

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| **Recommendation**  **Should Isoflurane & Nitrous Oxide vs. Nitrous oxide alone be used for critically ill adults undergoing a procedure (2.1)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ● | ○ | ○ | ○ |

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| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ● | ○ | ○ | ○ |
| **Recommendation** | We recommend not using inhalation of isoflurane for pain control during chest tube removal.  Consider other less invasive, less costly, and more studied interventions for chest tube removal pain. | | | |
| **Justification** | The effectiveness of this intervention for chest tube removal pain is only based on this one study with a sample of 35 patients.  Outcomes were not clearly reported. | | | |
| **Subgroup considerations** | The study was conducted in cardiac surgery patients. | | | |
| **Implementation considerations** | See under, "Are the resources required small?", above.  Not feasible to implement. | | | |
| **Monitoring and evaluation** | Evaluate patient pain before and after chest tube removal procedure as a factor of use of an analgesic intervention. | | | |
| **Research possibilities** | Pursue other types of analgesic interventions. | | | |

**Question**: A narcotic compared to an NSAID for critically ill adults undergoing a procedure (2.1)

**Setting**:

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **a narcotic** | **an NSAID** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain Score | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | very serious a | none | 17 | 19 | - | MD **0.45 lower** (2.16 lower to 1.26 higher) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations a. Wide confidence intervals don't exclude harm or benefit and small number of patients.

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| **Question** | | | | | |  |
| Should a narcotic vs. an NSAID be used for critically ill adults undergoing a procedure (2.1)? | | | | | |
| Population: | | critically ill adults undergoing a procedure (2.1) | | Background: |  |
| Intervention: | | a narcotic | |  |
| Comparison: | | an NSAID | |  |
| Main outcomes: | | * Pain Score | |  |
| **Assessment** | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | **Additional considerations** | |
| Problem | **Is there a problem priority?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes |  |  | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ○ Very low  ● Low | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Pain Score | CRITICAL | ⨁⨁◯◯ LOW | | One single study (Puntillo & Ley, 2004) [23]: 74 patients randomized in a double-blind study: 1) 4 mg of IV morphine + procedural information (n=17); 2) 30 mg of IV ketorolac + procedural information (n=19); 3) 4 mg of IV morphine + procedural + sensory information (n=19), and 4) 30 mg of IV ketorolac + procedural + sensory information (n=19). No control group included.  Procedure: CRT in cardiac surgery ICU patients  0-10 NRS pain intensity scores did not differ significantly across time among the 4 groups (RM-ANOVA F=0.82, p=0.49). Baseline pain scores (varied from 2.24 to 3.45), immediately after CTR (varied from 1.63 to 4.40), and 20 minutes after CTR (varied from 0.63-1.85). Self-reported pain scores appeared lower in Group 2 and Group 4 (but were not statistically significant). MD was 0.45 lower.  **Are the desirable effects large?**  Probably no because the MD was small. Effect size was also very small (0.03 for pain intensity).  **Are the undesirable anticipated effects small?**  Uncertain because they were not documented in this study.  **Are the desirable effects large relative to undesirable effects?**  Uncertainty because the desirable effects were small, and undesirable effects unknown. | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ● No important uncertainty or variability |
| **Are the desirable anticipated effects large?** | | ● Probably no |
| **Are the undesirable anticipated effects small?** | | ○ No  ○ Probably no  ● Uncertain |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ○ Probably no  ● Uncertain |
| Resource use | **Are the resources required small?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies |  | Yes because IV morphine and IV ketorolac are part of standard of care, and easily accessible for administration. | |
| **Is the incremental cost small relative to the net benefits?** | | ○ No  ○ Probably no  ● Uncertain |  | Probably yes because both treatments are easily accessible and seem to have similar effects. However, pain intensity was mild in all groups.  JF: Both treatments are inexpensive.  Paul: Benefits are uncertain.  Bram: Uncertain better in this case. | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes |  | Yes because these drugs are already part of ICU standard of care. | |
| Feasibility | **Is the option feasible to implement?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | Probably yes because to time the peak effect of medication with CTR can be difficult in practice (i.e., uncertainty about the time of CTR procedure). | |

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| **Recommendation**  **Should a narcotic vs. an NSAID be used for critically ill adults undergoing a procedure (2.1)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

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| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation** | We suggest offering either IV morphine or IV ketorolac prior to a procedure (i.e., CTR) for pain management in ICU patients (+2C).  should we keep general terms (opioid, NSAID)?  for procedures, can we extrapolate to any procedure?  question of interest to clinicians (for any procedure). | | | |
| **Justification** | The study findings did not confirm the relative superiority of either morphine or ketorolac as an analgesic prior to CTR. Pain intensity was mild in all groups. | | | |
| **Subgroup considerations** | CTR in cardiac surgery ICU patients | | | |
| **Implementation considerations** | Timing the administration of analgesia (peak effect) prior to the procedure is a key aspect to maximize effective pain reduction. Coordination with the care team is important (and can be challenging). | | | |
| **Monitoring and evaluation** | Pain assessment pre and post procedure to allow the evaluation of the effectiveness of analgesia.; monitoring of adverse events is also important to plan. | | | |
| **Research possibilities** | Include a control group and larger sample size; investigate other procedures and other medication (opioids, NSAID) in various ICU patient groups.  Implementation studies are also needed | | | |
| **Comments during electronic voting by entire panel** | The recommendation’s wording differs from the question – realizing it’s hard to make firm statements with low quality of evidence. Please qualify for "patients with normal kidney function not at risk of AKI" Recommendation & e to d table inconsistent; e to d recommends narcotic not nsaid; Recommendation based on one study with ketorolac, generalizing it to all NSAIDS and all procedures. | | | |

**Question**: NSAID gel compared to placebo for critically ill adults undergoing a procedure (2.1)

**Setting**:

**Bibliography**:

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **NSAID gel** | **placebo** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain Score | | | | | | | | | | | | |
| 1 | randomised trials | not serious | not serious | not serious | serious a | none | 53 | 53 | - | MD **3 lower** (3.56 lower to 2.44 lower) | ⨁⨁⨁◯ MODERATE | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations a. Lowered for small number of patients despite tight confidence intervals showing benefit.

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| **Question** | | | | | | | |  |
| Should NSAID gel vs. placebo be used for critically ill adults undergoing a procedure (2.1)? | | | | | | | |
| Population: | | critically ill adults undergoing a procedure (2.1) | | Background: | | |  |
| Intervention: | | NSAID gel | |  | | |
| Comparison: | | placebo | |  | | |
| Main outcomes: | | * Pain Score | |  | | |
| **Assessment** | | | | | | | | |
|  | **Criteria** | | **Judgements** | | **Research evidence** | **Additional considerations** | | |
| Problem | **Is there a problem priority?** | | ● Yes | |  |  | | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ● Moderate | | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Pain Score | CRITICAL | ⨁⨁⨁◯ MODERATE | | Singh study [24] :  Doubleblind RCT of cardiac patients with mediastinal and pleural chest tubes. Control:  paraffin gel around chest tubes (either mediastinal or pleural) (n=53) vs. 50 mg valdecoxib around chest tubes (either mediastinal or pleural) (n=53) at least 30 minutes prior to CTR (median 45 minutes).  0-10 VAS scores:  control 5 +1.48 vs valdecoxib 2 + 1.48 (p<0.05)  **SMD**: -3 [-3.56, -2.44]  **Desirable effects large?**  clinically significant differences in pain scores  **Undesirable effects small?**  no differences in HR, BP and other  "adverse effects" such as skin irritation. | | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ● No important uncertainty or variability | |
| **Are the desirable anticipated effects large?** | | ● Yes | |
| **Are the undesirable anticipated effects small?** | | ● Yes | |
| **Are the desirable effects large relative to undesirable effects?** | | ● Yes | |
| Resource use | **Are the resources required small?** | | ● Varies | |  | Application of NSAID around tube 30 minutes prior to CTR should not be too time intensive.  Probably more costly than opioids, although authors said cost for 10 g Valdecoxib would cost US $0.50.  - No gel available at the bedside in the US. - very expensive ($200/patient).  -: How to address availability issues? To be discussed in a larger forum. US cost to consider?  What is the cost of voltaren local analgesic gel?  -: Varies based on availability issues in different countries. | | |
| **Is the incremental cost small relative to the net benefits?** | | ● Varies | |  | Net benefits were large, availability and costs will vary. | | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ● Varies | |  | Stakeholders could accept depending on availability and cost. | | |
| Feasibility | **Is the option feasible to implement?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ● Varies | |  | With time, practice of applying NSAID gel would become routinized.  -: Varies based on options available in hospitals.  -: Initially Probably yes if available and at low cost, but varies is acceptable. | | |

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| --- | --- | --- | --- | --- | --- |
| **Recommendation**  **Should NSAID gel vs. placebo be used for critically ill adults undergoing a procedure (2.1)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ○ | ○ | ● |

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| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation** | Study results show clinically significant effects on CTR pain.  Application to practice is recommended.  We suggest offering using NSAID gel (if available) over placebo prior to CTR.  Small sample size + uncertainty, change for "we suggest offering this option". Vote to come  Very expensive product; no direct comparison besides placebo.  NSAID gel available available over the counter in France (not in the USA - Paul). | | | |
| **Justification** | CTR pain is substantial and needs effective intervention  One study from India with a product not available in the US. | | | |
| **Subgroup considerations** | Study conducted in India; needs replication in heterogeneous group of patients elsewhere and in patients with chest tubes after thoracic surgery or trauma, and in larger sample sizes. | | | |
| **Implementation considerations** | Gel needs to be applied long enough prior to procedure (30 to 60 minutes) to get peak effect.  Availability and costs to be taken into consideration. | | | |
| **Monitoring and evaluation** | Systematic assessment of pain scores before and during/after CTR. | | | |
| **Research possibilities** | See subgroup considerations. Other studies testing other products available in other countries. | | | |
| **comments during electronic Voting by Entire panel** | The recommendation is inconsistent with the e to d profile, which recommends nsaid gel | | | |

**Question**: Cold therapy compared to no cold therapy for critically ill adults undergoing a procedure (2.2)

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **cold therapy** | **no cold therapy** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain Intensity during Procedure (assessed with: 2 mins post procedure) | | | | | | | | | | | | |
| 2 | randomised trials | not serious | not serious | serious a | serious b | none | 65 | 65 | - | MD **1.91 lower** (5.34 lower to 1.52 higher) | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. Multiple time points after chest tube removal studied and only 2 mins post was significantly different (these are results presented here).

b. Small number of patients and confidence intervals do not rule out harm.

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| **Question** | | | | | | |  |
| Should cold therapy vs. no cold therapy be used for critically ill adults undergoing a procedure (2.2)? | | | | | | |
| Population: | | critically ill adults undergoing a procedure (2.2) | | | Background: |  |
| Intervention: | | cold therapy | | |  |
| Comparison: | | no cold therapy | | |  |
| Main outcomes: | | * Pain Intensity during Procedure | | |  |
| **Assessment** | | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | | **Additional considerations** | |
| Problem | **Is there a problem priority?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies | 10/12/16  Dear MA Heidari Gorji,   I am a member of a Guidelines panel on Pain, Agitation , Delirium, Early Mobilization and Sleep for the Society of Critical Care Medicine.  I read your report on ice packs for chest tube removal pain with great interest, and we would like to include it in our evidence results.  However, we have some questions about your study that I hope you can answer.   1)       Can you present the numbers in your sample?  We are confused as to whether 80 post-cardiac surgery patients were in the study (abstract).  Under Materials and Methods, you write that the sample size of 30 patients in each group (intervention and control) was increased to 40 in each group.  In this same section, in the paragraph that begins with “On the first day after operation”,  you describe assignment of patients to groups which is confusing to me.  Under Statistical Analysis, you say there were 90 patients for whom data were available.  Earlier you had said there were 80 patients.  In Table 1, I count 40 (male and female) patients in the experimental group and 40 (male and female)patients in the control group.  Regarding Table 2, how many patients were in each of the three groups:  control, cold application, and relaxation?  2)      Regarding the pain measurement tool that you used:  Under Materials and Methods, in the paragraph that begins with “Data collection tools…”, you write that you used a 0 – 100 mm Visual Analogue Scale.  However, in Table 2, you report pain severity scores as 4.6+0.66 (control) vs 2.4+0.52 (cold application) vs 2.3+0.35 (relaxation).  Are those scores on a 0 – 100 VAS or a 0 – 10 numeric rating scale (NRS)?  In Figure 1, your “y” axis is 0 – 5.  Was that per a 0 – 100 VAS or a 0 – 10 NRS?  3)      Do you provide differences in pain scores according to the type of chest tube removed, mediastinal or pleural?   Thank you for your help with this. | | Non-pharmacological interventions for pain management  are important in the ICU and could contribute to reduce pain and to improve pain control in patients. | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ○ Very low  ● Low  ○ Moderate  ○ High | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Pain Intensity during Procedure | CRITICAL | ⨁⨁◯◯ LOW | | | **Overall Certainty:**2 studies were in data abstraction. Gorji 2014 [25] was true RCT and Sauls 2002 [26] was before and after study. The results were different (Gorji showed benefit whereas Sauls did not). In Gorji[25] , for intervention group #1, iced packs wound around chest tube x 10 minutes until temperature 13 degrees; for intervention group #2, relaxation: calm and deep breathing for 5 minutes, then 10 minutes more; control group#3 received no intervention.  Used 0 - 100 VAS ***but must have reported on a 0 - 10 scale.***  *Pain intensity scores immediately after CTR:*  *cold application group = 2.4 + 0.52*  *control group = 4.6 + 0.66*  ***Size of each of the groups unknown.  See email.***  **Gorji:  SMD 3.67 [-4.40, -2.94] lower for cold therapy; Significant**  In Sauls[26] , for intervention group, ice pack on either side of chest tube for 10 minutes; for control group, tepid water pack on either side of chest tube. Used 0 - 10 NRS.  *Pain intensity scores immediately after CTR:*  *Control group (n=25):  6.34  + 2.52*  *experimental group (n=25):  5.86 + 2.82*  **Sauls:  SMD -0.17 lower for cold therapy [-0.72, 0.39] NS**  **Are the desirable anticipated effects large?**  The overall SMD is -1.91 [-5.34, 1.52]  Therefore, the desirable anticipated effects are probably large because a NRS pain intensity difference greater than 1.7 - 2 is assessed as clinically significant.  However, this was from only 1 study with a questionable sample size.  Group consensu  **Are the undesirable anticipated effects small?** There was no mention in either study of side effects associated with the use of cold packs.  But it is possible that patients could have skin burns from cold packs if applied directly to skin for too long.  No evidence of side effects, so uncertain. Burn injury not negligable.  - Uncertain  **Are the desirable effects large relative to undesirable effects?** There was a significant decrease in pain in Gorji's cold pack group, with no reports of undesirable effects. | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ○ Important uncertainty or variability  ○ Possibly important uncertainty or variability  ○ Probably no important uncertainty or variability  ● No important uncertainty or variability |
| **Are the desirable anticipated effects large?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |
| **Are the undesirable anticipated effects small?** | | ○ No  ○ Probably no  ● Uncertain |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |
| Resource use | **Are the resources required small?** | | ○ No  ○ Probably no  ● Uncertain | No description of resources besides the gel packs in studies. | | Three cooling gel packs (8 × 10 cm) twisted in gauze were used to wrap around each chest tube for 10 minutes prior to tube removal.   These packs would have to be purchased and stored in a freezer in the ICU.  Having enough room for more than one set may pose a problem. | |
| **Is the incremental cost small relative to the net benefits?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | | The overall costs of the gel cooling packs should be incidental if the benefits to patients were decreased pain associated with a procedure known to cause substantial pain.  Patients who had received opioid analgesic during less than 4 hours before the intervention were excluded from the study.  However, costs of an analgesic intervention, if needed to augment cold therapy, would be low. | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | | Key stakeholders should be committed to a relatively low cost, non-pharmacological approach to pain relief. | |
| Feasibility | **Is the option feasible to implement?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | | Implementation would require a practice change and development of a written protocol for use of the gel packs, as well as purchase and storing of the gel packs.  -Uncertain: only 2 studies with contradictory results. In one study, patients did not receive opioids.  - Probably yes; question on feasibility of implementing of the intervention.  - Feasible to implement considering the low amount of resources needed compared to other interventions. | |

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| **Recommendation**  **Should cold therapy vs. no cold therapy be used for critically ill adults undergoing a procedure (2.2)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ○ | ● | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation** | We suggest to offer cold therapy during chest tube removal for ICU pain management (to be confirmed).  More research is needed, with inclusion of larger samples, before the use of cold gel packs is determined to be efficacious for pain relief during chest tube removal.  Note: Still waiting to hear from Gorji to answer our questions. | | | |
| **Justification** | Chest tube removal pain was decreased in one study of cold packs. | | | |
| **Subgroup considerations** | These 2 studies were conducted with cardiac surgery patients.  In Gorji study, patients had 1 mediastinal tube and 1 left pleural tube.  Differences in pain between the 2 types of tubes were not reported.  In previous research, (Puntillo & Weiss, 1994) [27], pleural chest tubes were significantly more painful than mediastinal tubes.  So, type of tube should be analyzed. | | | |
| **Implementation considerations** | Implementation would require a practice change in a particular ICU. | | | |
| **Monitoring and evaluation** | Pre and post pain assessments to evaluate impact of the intervention. Patient's preference and satisfaction to be considered. | | | |
| **Research possibilities** | The Gorji [25] study was conducted in Iran. Other patient groups, such as those with chest tubes after thoracic surgery or after trauma, should be studied.  Mechanically ventilated patients were excluded from the Gorji [25] study.  Those patients could be included in future studies and, if they are unable to self-report pain, a pain behavior scale could be used to assess pain.  These steps could increase generalizability of study results.  If patients reported pain prior to the procedure, they could be medicated with analgesic drugs, and the effect of these drugs, as well as the ice, could be examined | | | |
| **Comments during electronic voting by entire panel** | Unclear whether cold/ music therapy offered as sole pain management strategy or considered adjuncts from the question.  Evidence poor; RCT study= beneficial, pre-post negative, gaps in methods/ results and methods. | | | |

**Question**: Relaxation with pharmacotherapy compared to no relaxation for critically ill pain management (5.4)

| **Quality assessment** | | | | | | | **№ of patients** | | **Effect** | | **Quality** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Relaxation with pharmacotherapy** | **no relaxation** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Pain Intensity immediately after Chest Tube Removal (VAS cm) | | | | | | | | | | | | |
| 2 | observational studies | not serious a | serious b,c | not serious | very serious d,e | none | 31 | 33 | - | MD **0.32 higher** (0.67 lower to 1.31 higher) | ⨁◯◯◯ VERY LOW | CRITICAL |
| Pain intensity 15 minutes after Chest tube removal (VAS cm) | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | serious d,f | none | 19 | 21 | - | MD **2.5 lower** (4.18 lower to 0.82 lower) | ⨁◯◯◯ VERY LOW | CRITICAL |

**CI:** Confidence interval; **MD:** Mean difference

#### Explanations

a. 1 study indicated low risk of bias; 2nd study indicated high ROB due to variable co-interventions between groups and no adjustment for group differences

b. 1 study showed variable results based on gender and age; results not consistent amongst groups

c. I2 = 80%

d. Low sample size

e. mean difference crosses line of no effect

f. Despite CI that do not cross 'no effect', imprecision lowered for sample size

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Question** | | | | | | |  |
| Should Relaxation with pharmacotherapy vs. no relaxation be used for critically ill pain management (5.4)? | | | | | | |
| Population: | | critically ill pain management (5.4) | | Background: | |  |
| Intervention: | | Relaxation with pharmacotherapy | |  | |
| Comparison: | | no relaxation | |  | |
| Main outcomes: | | * Pain Intensity immediately after Chest Tube Removal (VAS cm) * Pain intensity 15 minutes after Chest tube removal (VAS cm) | |  | |
| Setting: | |  | |  | |
| Perspective: | |  | |  | |
| **Assessment** | | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | **Additional considerations** | | |
| Problem | **Is there a problem priority?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes |  | Non-pharmacological interventions for pain management are important in the ICU and could contribute to reduce pain and to improve pain control in patients. | | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ● Very low | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Pain Intensity immediately after Chest Tube Removal (VAS cm) | CRITICAL | ⨁◯◯◯ VERY LOW | | Pain intensity 15 minutes after Chest tube removal (VAS cm) | CRITICAL | ⨁◯◯◯ VERY LOW | | **Summary of overall evidence on pain scores:**  2 matched cohort studies (Friesner et al. 2006; Houston & Jesurum, 1999) [28, 29] in which pain scores were higher immediately after CTR with a MD of 0.32, and then decreased with a MD of 2.5 15 minutes after CTR. However, the quality of evidence was very low. Small samples were used in both studies (n=40 and 24, respectively).  In Friesner et al. (2006) (n=40), relaxation consisted of deep-breathing exercises. Immediately after CTR, mean pain scores were 6.57 (SD=2.61) for the intervention group, and 8.61 for the control group (SD=2.96). Mean pain scores decreased to 3.07 (SD=2.45) and to 5.57 (SD=2.96) in the intervention group, and the control group respectively. Significant decreases in pain scores with relaxation were found immediately after, and 15 minutes post CTR (F tests, p<0.01) (p. 273).  In Houston & Jesurum (1999) [29] (n=24), the quick relaxation technique (QRT) consisted of clenching fists, deep breathing, go limp as a rag doll, and yawning. Strange results were obtained and were presented by age and gender. In summary, pain scores were not significantly different between groups (p=0.062). Men older than 70 yo in the control group showed almost twice more pain than those of the intervention group. The situation was reversed in older women (p.202).  **Are the desirable anticipated effects large?**  Likely uncertain, 2 non RCTs with small samples and very low quality of evidence. Opioid administration was variable between patients.  **Are the undesirable anticipated effects large?**  No mention of adverse events in both studies.  **Are the desirable effects large relative to undesirable effects?**  Uncertain based on very low evidence and no information on adverse events (although they appear to be very unlikely). | | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ● No important uncertainty or variability |
| **Are the desirable anticipated effects large?** | | ○ No  ○ Probably no  ● Uncertain |
| **Are the undesirable anticipated effects small?** | | ● Probably yes |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ○ Probably no  ● Uncertain |
| Resource use | **Are the resources required small?** | | ○ No  ○ Probably no  ○ Uncertain  ○ Probably yes  ● Yes  ○ Varies | Instructions clearly described in both studies. | Short instructions which can be taught to ICU patients at the bedside. | | |
| **Is the incremental cost small relative to the net benefits?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | Is relaxation worth the benefit?  The net benefits remain to be demonstrated, but appear promising. Relaxation does not involve any cost. | | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | I would believe that the vast majority would likely approve this intervention.  Patient's preference to take into consideration. | | |
| Feasibility | **Is the option feasible to implement?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes | No implementation studies available.  In Friesner et al. (2006)[28] , the relaxation techinique was initiated by patients 5 minutes before CTR.  In Houston & Jesurum (1999)[29] , the quick relaxation technique was taught to patients the day prior to CTR, and participated in two practice sessions (one immediately prior to CTR). | Little resource and time needed to perform a brief relaxation technique during procedural pain.  Minimal training required.  Nursing training?  Will depend on relaxation technique. | | |

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| **Recommendation**  **Should Relaxation with pharmacotherapy vs. no relaxation be used for critically ill pain management (5.4)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ● | ○ | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation** | We suggest offering relaxation during procedural pain as a complementary intervention to ICU pain management (+2C).  Can we still suggest an intervention if the benefits and consequences are balanced or uncertain?  Do we change to probably outweigh? | | | |
| **Justification** | Although evidence is of very low quality, relaxation remains a safe and quick intervention to use. However, the benefits remain to be demonstrated. Worth mentioning, various relaxation techniques were used in included studies. | | | |
| **Subgroup considerations** | Both included studies were performed in cardiac surgery (CABG) ICU patients during CRT (chest tube removal). | | | |
| **Implementation considerations** | No specific resources needed to apply this intervention. Minimal training required. Written information could also be provided to patients to get familiar with relaxation. | | | |
| **Monitoring and evaluation** | Pre and post pain assessments to evaluate impact of the intervention. Patient's preference and satisfaction could also be considered. | | | |
| **Research possibilities** | Experimental studies (RCT) are clearly needed to demonstrate the benefits of relaxation. Implementation studies are also lacking. | | | |

**Question**: Standardized and/or protocol-based analgesia/analgosedation programs compared to no standardized programs for critical care pain management (4)

**Setting**: Critical Care ICU

**Bibliography**:

| **Quality assessment** | | | | | | | | **№ of patients** | | | | **Effect** | | | | **Quality** | | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Incon-sistency** | **Indirect**  **-ness** | **Imprec-**  **ision** | **Other considerations** | | **standardized and/or protocol-based analgesia/analgosedation programs** | | **no standardized programs** | | **Relative (95% CI)** | | | **Absolute (95% CI)** |
| Nosocomial infection | | | | | | | | | | | | | | | | | | |
| 2 | randomised trials | serious a | not serious | not serious b | serious c,d | none | | 6/112 (5.4%) | | 10/106 (9.4%) | | RR 0.62 (0.25 to 1.56) | | | **36 fewer per 1,000** (from 53 more to 71 fewer) | ⨁⨁◯◯ LOW | | CRITICAL |
| Duration of MV | | | | | | | | | | | | | | | | | | |
| 3 | randomised trials | serious e | not serious | not serious | not serious | none | | 313 | | 326 | | - | | | MD **1.26 lower** (1.8 lower to 0.73 lower) | ⨁⨁⨁◯ MODERATE | | CRITICAL |
| ICU LOS | | | | | | | | | | | | | | | | | | |
| 3 | randomised trials | serious e | not serious | not serious | not serious | none | | 313 | | 326 | | - | | | MD **2.27 lower** (2.96 lower to 1.58 lower) | ⨁⨁⨁◯ MODERATE | | CRITICAL |
| Constipation | | | | | | | | | | | | | | | | | | |
| 1 | observational studies | not serious | not serious | not serious | serious d | none | 18/50 (36.0%) | | 15/50 (30.0%) | | RR 1.20 (0.68 to 2.11) | | | **60 more per 1,000** (from 96 fewer to 333 more) | | ⨁◯◯◯ VERY LOW | | IMPORTANT |
| Cardiovascular Adverse Drug Reaction | | | | | | | | | | | | | | | | | | |
| 2 | randomised trials | serious f | not serious | not serious b | serious d | none | 4/153 (2.6%) | | 4/157 (2.5%) | | RR 0.90 (0.26 to 3.14) | | **3 fewer per 1,000** (from 19 fewer to 55 more) | | | | ⨁⨁◯◯ LOW | CRITICAL |
| Sedatives Exposure | | | | | | | | | | | | | | | | | | |
| 1 | randomised trials | serious g | not serious | not serious | serious c | none | 110 | | 116 | | - | | SMD **0.57 lower** (0.84 lower to 0.31 lower) | | | | ⨁⨁◯◯ LOW | CRITICAL |
| Opioid Exposure | | | | | | | | | | | | | | | | | | |
| 1 | randomised trials | serious g | not serious | not serious | serious c | none | 55 | | 58 | | - | | MD **0.06 SD higher** (0.31 lower to 0.42 higher) | | | | ⨁⨁◯◯ LOW | CRITICAL |
| Pain intensity VAS (cm) | | | | | | | | | | | | | | | | | | |
| 4 | observational studies | not serious | not serious | not serious | not serious | none | 747 | | 780 | | - | | MD **0.35 lower** (0.49 lower to 0.22 lower) | | | | ⨁⨁◯◯ LOW | CRITICAL |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

#### Explanations

a. 1 study reports no blinding of participants or outcome assessors; the other study does not report randomization or blinding processes

b. Note: only includes remifentanil based analgosedation protocols

c. Small sample size

d. Unclear if benefit or harm

e. Two studies report randomization; 1 study did not report randomization; no studies had adequate blinding of participants or outcome assessors

f. 1 study did not clearly report randomization or blinding of participants/assessors; 2nd study did not randomize or blind participants/assessors

g. Appropriate randomization and intention-to-treat, however inadequate or lack of randomization

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Question** | | | | | | |  |
| Should standardized and/or protocol-based analgesia/analgosedation programs vs. no standardized programs be used for critical care pain management (4)? | | | | | | |
| Population: | | critical care pain management (4) | | Background: | |  |
| Intervention: | | standardized and/or protocol-based analgesia/analgosedation programs | |  | |
| Comparison: | | no standardized programs | |  | |
| Main outcomes: | | * Nosocomial infection * Duration of MV * ICU LOS * Constipation * Cardiovascular Adverse Drug Reaction * Sedatives Exposure * Opioid Exposure * Pain intensity VAS (cm) | |  | |
| Setting: | | Critical Care ICU | |  | |
| **Assessment** | | | | | | | |
|  | **Criteria** | | **Judgements** | **Research evidence** | **Additional considerations** | | |
| Problem | **Is there a problem priority?** | | ● Yes |  |  | | |
| Benefits & harms of the options | **What is the overall certainty of this evidence?** | | ○ No included studies  ○ Very low  ● Low | **The relative importance or values of the main outcomes of interest:**   | **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** | | --- | --- | --- | | Nosocomial infection | CRITICAL | ⨁⨁◯◯ LOW | | Duration of MV | CRITICAL | ⨁⨁⨁◯ MODERATE | | ICU LOS | CRITICAL | ⨁⨁⨁◯ MODERATE | | Constipation | IMPORTANT | ⨁◯◯◯ VERY LOW | | Cardiovascular Adverse Drug Reaction | CRITICAL | ⨁⨁◯◯ LOW | | Sedatives Exposure | CRITICAL | ⨁⨁◯◯ LOW | | Opioid Exposure | CRITICAL | ⨁⨁◯◯ LOW | | **are the desirable anticipated effects large?**  **reduction in duration of MV and reduction in ICU LOS(data from 3 RCTs)**  Duration of MV = MD - 1.26 (-1.8 to -0.73)  ICU LOS = MD -2.27 (-2.96 to -1.58)  Rozendaal FW, Spronk PE, Snellen FF, et al: Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: A centre randomised, cross-over, open-label study in the netherlands. Intensive Care Med 2009;35:291-298 [30]  Brook AD, Ahrens TS, Schaiff R, et al: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999;27:2609-2615 . [31]  Strom T, Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: A randomised trial. Lancet 2010;375:475-480  **Pain intensity - "reduced" 4 cohort trials NRS (0-10) - pooar**  burns. Burns 2010;36:639-646 [32]  undergoing cardiac surgery after implementation of a quality improvement postoperative pain treatment program. J Crit Care 2008;23:359-371 [33]   Egerod I, Jensen MB, Herling SF, et al: Effect of an analgo-sedation protocol for neurointensive patients: A two-phase interventional non-randomized pilot study. Crit Care 2010;14:R71 [34]  Skrobik Y, Ahern S, Leblanc M, et al: Protocolized intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. Anesth Analg 2010;111:451-463 [35]  **nosocomial infection** - no difference combining 2 RCT  RR 0.62 (0.25 to 1.56)  36 fewer per 1000 patients  Breen D, Karabinis A, Malbrain M, et al: Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: A randomised trial [ISRCTN47583497]. Crit Care 2005;9:R200-10 [36]   Strom T,  Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: A randomised trial. Lancet 2010;375:475-480) [37]  Discussion:  JF: Yes considering effects on MV duration and ICU LOS  Celine + Kathleen: Probably yes considering no clinical significance on pain scores (refer to question)  Gerald: Yes - protocol with sedatives which impact on patient's LOC so more impact on other outcomes than pain intensity  Use of sedatives and analgesics will influence pain scores - Berger trial (1.4 control vs 0.9 intervention), 2.7 control vs 1.4 protocol,  1.61 control vs 1.15 protocol, 1.5 vs 0.6  So pain scores were low (average over the ICU LOS) in both groups and the differences was still significant - could change to Yes based on this information  **are the undesirable anticipated effects small?**  **constipation  - no difference**  (although only 1 cohort trial assessed it - Bowel movement at 48 hours)  RR 1.20 (0.68 to 2.11)  60 more per 1000 pt  Tedders KM, McNorton KN, Edwin SB: Efficacy and safety of analgosedation with fentanyl compared with traditional sedation with propofol. Pharmacotherapy 2014;34:643-647  **Cardiovascular ADR**no difference (2RCT)  RR 0.90 (0.26 to 3.14)  3 fewer per 1000 pt  Breen D, Karabinis A, Malbrain M, et al: Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: A randomised trial [ISRCTN47583497]. Crit Care 2005;9:R200-10 [36]  Rozendaal FW, Spronk PE, Snellen FF, et al: Remifentanil-propofol analgo-sedation shortens duration of ventilation and length of ICU stay compared to a conventional regimen: A centre randomised, cross-over, open-label study in the netherlands. Intensive Care Med 2009;35:291-298 [30]  **Sedation exposure -reduced (1 RCT) - reduced**  SMD - 0.57 (-0.84 to -0.31)   Strom T,  Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: A randomised trial. Lancet 2010;375:475-480) [37]  **Opioid exposure - (1 RCT) no difference**  +0.06 (-0.31 to +0.42)   Strom T,  Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: A randomised trial. Lancet 2010;375:475-480) [37] | | |
| **Is there important uncertainty about how much people value the main outcomes?** | | ● No important uncertainty or variability |
| **Are the desirable anticipated effects large?** | | ● Yes |
| **Are the undesirable anticipated effects small?** | | ● Probably yes  ○ Yes  ○ Varies |
| **Are the desirable effects large relative to undesirable effects?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |
| Resource use | **Are the resources required small?** | | ○ No  ● Probably no  ○ Uncertain  ○ Probably yes  ○ Yes  ○ Varies |  | can be a big practice change to end users. May require more resources  implementing protocols can be time consuming and maintaining the quality is challenging  : agree  : Probably no or varies - resources are variable from an ICU to another | | |
| **Is the incremental cost small relative to the net benefits?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes  ○ Yes  ○ Varies |  | Reduction in ICU LOS drives economics, however it is important to note the  implementation typically requires dedicated support.  there MAY be an increase need for 1:1 nursing care (or use of sitters - leave out?)  In addition,  it is important to note some of the cohort trials and some of the RCT utilize remifentanil. This question does not cull out individual medications; therefore the cost of specific medication should not influence cost.  comment on use of sitters (could be seen as a cost barrier) - may be related to more agitation  less sedatives, more awake patients may lead to increased presence at the bedside  In some countries the ratio of nurse-pt is 1:1 (nurse also manage the ventilator); more mobilization too specific to one study | | |
| Acceptability | **Is the option acceptable to key stakeholders?** | | ○ No  ○ Probably no  ○ Uncertain  ● Probably yes |  | Standardized and/or protocol-based analgesia/analgosedation programs can be polarizing topic. Some multi-professional ICU leaders are very supportive and others are not.  Change to Probably yes - although we know that not all opioids are easily available in all countries  -Nurse satisfaction increased after implementation of such a protocol – prob.yes | | |
| Feasibility | **Is the option feasible to implement?** | | ● Probably yes |  | it's been done in several real-life cohort examples, therefore likely feasible (but not easy) Group agrees! | | |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Recommendation**  **Should standardized and/or protocol-based analgesia/analgosedation programs vs. no standardized programs be used for critical care pain management (4)?** | | | | | |
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|  | ○ | ○ | ○ | ● | ○ |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|  | ○ | ○ | ● | ○ |
| **Recommendation** | We suggest standardized and/or protocol-based analgesia/analgosedation programs should be utilized for critical care pain management. (+2C)  \*3 RCTs with consistent results; suggest to change with "recommend" (Kathleen agrees)  \*refer to 2013 guidelines (suggest) because it was a +2B  \*C for low quality of evidence so should be +2C  \*Recommend has a stronger impact on policy makers - it would require that all ICUs have protocols for their patients - does not mean that pain not be managed it can be done individually  \*agrees with "recommend" but also with consistency with previous guidelines  Paul: stay with "suggest"  \*analgosedation defined as "analgosedation refers to the use of opioids for pain control and sedation purposes." by the group | | | |
| **Justification** | Reduction in ICU LOS and MV with no apparent increase in ADE (adverse drug events) compared to standard of care. | | | |
| **Subgroup considerations** | Many subgroups have been studied, however much more research in need (see research possibilities below) in specific ICU population. Neuro ICU, Trauma ICU, Cardiac Surgery ICU. | | | |
| **Implementation considerations** | Institutions should have have frequent assessment (multiple times a day) of pain via validated tools as a standard of care (patient report and behavioral pain scores). Leaders need to be willing to champion the effort to embrace the challenges of implementing clinical practice change. | | | |
| **Monitoring and evaluation** | Important to monitor process measures (e.g. quality of pain assessment documentation, compliance with frequency, opioid/sedation mediation utilization) and clinical outcomes (e.g. pain scores, ICU LOS, length of MV) as well as economic impact. | | | |
| **Research possibilities** | is one opioid better than another for standardized and/or protocol-based analgesia/analgosedation programs ? Gerald - clearly define analgesia-based sedation Is there an ICU setting (ICU patient population) most appropriate for standardized and/or protocol-based analgesia/analgosedation programs?  Is the benefit of standardized and/or protocol-based analgesia/analgosedation programs reduction in pain or is it avoidance of harmful sedatives?  More in depth look at the adverse effects, opioid withdrawal and post-hospital opioid use disorder associated with standardized and/or protocol-based analgesia/analgosedation programs. | | | |
| **Comments during electronic voting by entire panel** | Hesitant about strong recommendation; moderate evidence on ICU LOS and MV duration. With validated pain assessment tools available, it is time to move forward and implement structured pain management approaches. Comparative group needs to be added into the recommendation. "Assessment driven" is not in the question; qualifier warrants justification | | | |

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