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SUMMARY WITH CRITICAL APPRAISAL

Nociception Monitoring for General Anesthesia: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Authors: Srabani Banerjee, Danielle MacDougall

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ANI	Analgesia Nociception Index
ANS	Autonomous Nervous System
CARDEAN	Cardiovascular Depth of Analgesia
IoC	Index of Consciousness
NAN	nociception/anti-nociception
RCT	Randomized Controlled Trial
SPI	Surgical Pleth Index

Context and Policy Issues

General anesthesia is induced with the use of anesthetics which comprise analgesics, hypnotic agents and muscle relaxants.[1,2] Analgesics prevent autonomic and somatic responses, hypnotic agents prevent awareness, and muscle relaxants prevent reflex movements.[2] Careful monitoring of the effects of general anesthesia is needed to avoid under or over-dose of anesthetics, and hence prevent the associated complications and adverse effects.[3] Generally, hemodynamic parameters have been used to guide the intraoperative administration of analgesics such as opioids, however, hemodynamic parameters are not standardized and may not always provide a clear assessment.[4] There is a growing interest in the use of more effective monitoring of the analgesia component of anesthesia to guide administration of analgesics to achieve an appropriate nociception and anti-nociception (NAN) balance.[5,6]

Various monitoring techniques have been developed to assess the NAN balance. These techniques are based on analysis of the autonomous nervous system (ANS) reactions to a changing environment during anesthesia and surgery, and use physiological signals processing algorithms.[1] Most techniques use measures based on heart rate variability, heart frequency, vascular tone, or inhibition of cardiac baroreflex.[6] The Analgesia Nociception Index (ANI) is based on heart rate variability.[6] The technique based on ANI, measures the relative parasympathetic tone by continuously analyzing the influence of respiratory sinus arrhythmia on heart rate.[1] The Cardiovascular Depth of Analgesia (CARDEAN) index is based on stimulus induced increases of blood pressure and heart rate (somatic-sympathetic reflex) and is measured by a non-invasive continuous beat-to-beat blood pressure monitor.[6] The Surgical Pleth Index (SPI) is based on normalized plethysmographic derived heart rate and pulse wave amplitude.[6] SPI is computed from the signal received from a photoplethysmograhic sensor placed on the finger.[1] The nociception level indexes are based on a combination of multiple physiological parameters. A device was developed to assess nociception levels using a multi-parameter approach, and comprised a photoplethysmographic sensor and skin conductance electrodes combined in a single finger probe.[1] Pupillometry is used to study ANS sympathetic activity and measures changes in pupil diameter in response to different painful stimuli. A device was developed based on the pupil response to noxious stimuli. However, this technique has limited use as direct access to the eye is needed and the NAN balance can only be assessed intermittently.[1] No gold standard exists for the evaluation of NAN balance.[1] There appears to be uncertainty regarding the effectiveness of nociception monitoring techniques.

The purpose of this report is to review the clinical effectiveness and cost-effectiveness of nociception monitoring on pain, opioid/pain medication consumption and/or opioid-related adverse events in adult surgical patients who have undergone general anesthesia. Additionally, this report aims to review the evidence-based guidelines regarding the use of

nociception monitoring on pain, opioid/pain medication consumption and/or opioid-related adverse events in adult surgical patients who have undergone general anesthesia.

Research Questions

1. What is the clinical effectiveness of nociception monitoring on pain, opioid/pain medication consumption and/or opioid-related adverse events in adult surgical patients who have undergone general anesthesia?
2. What is the cost-effectiveness of nociception monitoring on pain, opioid/pain medication consumption and/or opioid-related adverse events in adult surgical patients who have undergone general anesthesia?
3. What are evidence-based guidelines informing the use of nociception monitoring on pain, opioid/pain medication consumption and/or opioid-related adverse events in adult surgical patients who have undergone general anesthesia?

Key Findings

There is a suggestion that in adult patients undergoing surgery under general anesthesia, the intraoperative opioid consumption is generally less with nociception monitoring compared with standard monitoring, however the between group differences were not always statistically significant.

There appears to be no statistically significant difference between nociceptive monitoring and standard monitoring with respect to intraoperative adverse events, postoperative opioid or analgesic consumption, postoperative pain, and postoperative adverse events.

Findings need to be interpreted in the light of limitations (such as a limited number of studies on each surgery type and anesthetic protocol, lack of detail regarding standard monitoring procedures, and not all relevant outcomes reported in all the studies).

No relevant evidence regarding the cost-effectiveness of and no evidence-based guidelines regarding nociceptive monitoring in adult patients undergoing surgery under general anesthesia were identified.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including MEDLINE, PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and November 14, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult (ages 18 and over) surgical inpatients who are undergoing and/or have undergone general anesthesia
Intervention	Nocicepetion monitoring (including the use of commercially available monitors and/or use of the nociception level (NoL) index)
Comparator	Standard care (i.e., monitoring based on hemodynamics, physiological parameters e.g., heart rate, respiratory rate, etc.)
Outcomes	Q1 - Clinical effectiveness, including benefit and/or harm i.e., ○ post-operative pain • e.g., resting and dynamic pain scores measured in the post-operative recovery unit (PACU) and the first postoperative day (POD1) ○ intra operative and/or post-operative opioid consumption • e.g., first 24-hour opioid consumption scores; PACU opioid consumption ○ post-operative consumption of multi-modal pain medications including: • e.g., Tylenol, naproxen, NSAIDs, gabapentin, etc. ○ intra-operative and/or post-operative, opioid-related adverse events • e.g., first 24 h incidence of nausea/vomiting, first 24 h incidence of pruritus Q2 - Cost-effectiveness • e.g., length of stay in hospital; reduced use of opioids Q3 - Guidelines i.e., evidence-based guidance and recommendations
Study Designs	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies (if only few health technology assessments, systematic reviews/meta-analyses), economic evaluations, and evidence-based guidelines

h = hour; NoL = nociception level; NSAIDs = non-steroidal anti-inflammatory drugs; PACU = post-operative recovery unit; POD1 = first postoperative day;

Exclusion Criteria

Articles were excluded if they did not the selection criteria outlined in Table 1, they were duplicate publications, or were published prior 2013.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR 2,[7] and RCTs were critically appraised using the Downs and Black checklist.[8] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each individual study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 383 citations were identified in the literature search. Following screening of titles and abstracts, 363 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 15 publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised two systematic reviews and three RCTs. No economic evaluations or evidence-based guidelines were identified. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study characteristics are summarized and details are provided in Appendix 2, Tables 2 and 3.

Study Design

Two relevant systematic reviews[6,9] were included. One systematic review[9] was published in 2018 and included a literature search period up to February, 2017. It included six RCTs that were published between 2010 and 2016. The second systematic review[6] was published in 2017, and included a literature search period up to April 2016. It included seven RCTs that were published between 2010 and 2015. There was some overlap in the RCTs included in these two systematic reviews; this overlap is presented in Appendix 5.

Three relevant RCTs[4,10,11] were included, of which two RCTs[10,11] were single blinded and in one RCT[4] blinding was not mentioned. One RCT[4] was published in 2017, one RCT[10] was published in 2016, and one RCT[11] was published in 2015.

Country of Origin

One systematic review[9] was published from South Korea and included three RCTs from Germany, one RCT from Italy and two RCTs from South Korea. The second systematic review[6] was published from Germany, and the countries for the included RCTs were not mentioned.

One RCT[4] was published from Turkey, one RCT[10] was published from Australia, and one RCT[11] was published from China.

Patient Population

Both systematic reviews[6,9] analyzed RCTs that included adults, with the exception of one RCT that included children, in each of the systematic reviews. Only characteristics for the adult population are presented in this review. The patients underwent various types of surgery and the numbers of adult patients were 418 in one systematic review[9] and 638 in one systematic review.[6] The age range was 18 to 70 years and the proportion of females ranged between 31% and 82% in one systematic review[9] and was not specifically reported in one systematic review.[6]

The three included RCTs[4,10,11] included adult patients undergoing surgery, the mean age varied between 47 years and 51 years, the mean weight varied between 70 kg and 85 kg, and the proportion of female patients varied between 54% and 100%. Two RCTs[4,10] included patients undergoing breast surgery and one RCT[11] included patients undergoing lumbar discectomy or laminectomy

Interventions and Comparators

For patients undergoing surgery under general anesthesia, one systematic review[9] compared SPI guided monitoring with standard monitoring procedures and the second systematic review[6] compared monitoring using various methods (SPI, ANI, or CARDEAN) with standard monitoring procedures.

For patients undergoing surgery under general anesthesia, two RCTs[4,10] compared ANI guided monitoring with standard monitoring procedures. The third RCT[11] compared monitoring guided by depth of anesthesia with monitoring not guided by depth of anesthesia. Depth of anesthesia was based on index of consciousness (IoC) which

comprises of two indices: IoC1 (index based on depth of sedation) and IoC2 (index based on depth of analgesia).

Outcomes

Both the systematic reviews[6,9] reported on intraoperative opioid consumption, intraoperative movement, intraoperative adverse events (hemodynamic events) and postoperative pain. In addition, one systematic review[9] reported on extubation time; and the second systematic review[6] reported on time to emergence, and postoperative opioid consumption.

All three RCTs[4,10,11] reported on intraoperative opioid consumption. One RCT[11] reported on intraoperative adverse events. Two RCTs[4,10] reported on duration of stay in recovery room, and pain during stay in recovery room. Two RCTs reported on postoperative adverse events.[10,11]

Summary of Critical Appraisal

Critical appraisal of the included studies is summarized below and details are presented in Appendix 3, Tables 4 and 5.

Systematic reviews

Both the included systematic reviews[6,9] stated the objective, and inclusion criteria; described the selection of articles; and included a list of included studies. In one systematic review[9] a comprehensive literature search using multiple databases was undertaken, whereas in one systematic review[6] a single database was searched. Searching multiple databases reduces the potential of missing articles. The article selection, data extraction and quality assessment were done in duplicated in one systematic review[9] and were unclear in one systematic review.[6] Duplication reduces the potential for errors and biases in article selection, data extraction, and quality assessment. In one systematic review[9] majority of the included studies appeared to be of good quality; and in the second systematic review[6] majority of the studies appeared to be above average quality. The quality assessment method was different in the two systematic reviews. The study characteristics were described in both systematic reviews but details were lacking in one systematic review.[6] In one systematic review,[9] exploring publication bias with a few studies was considered not feasible; and in one systematic review[6] method for examining publication bias was not described but it was stated that there was possibility of bias. In one systematic review[9] conflicts of interest were declared and there appeared to be no issue; and in one systematic review[6] conflicts of interest were declared and potential for bias could not be ruled out.

Randomized controlled trials

In all three RCTs[4,10,11] the objective, inclusion and exclusion criteria were stated; the patient characteristics, interventions and outcomes were described; and it was mentioned that the authors had no conflicts of interest. The randomization method appeared to be appropriate in two RCTs,[10,11] and was unclear in one RCT.[4] Two RCTs[10,11] were single blinded (patients were unaware of the type of monitoring), hence the patients' responses are unlikely to be influenced by their knowledge of the type of monitoring. In one single-blinded RCT,[10] though the anesthetists were not blinded, they were unaware of the post-operative results hence their actions would not be biased by results. In one single-blinded RCT,[11] it was unclear if the anesthetists were unaware of post-operative results hence it is unclear if their actions could be biased by results. Blinding was not mentioned in one RCT,[4] hence

potential for bias cannot be ruled out. In two RCTs[10,11] the sample size was determined and the appropriate sample size was used; and in one RCT[4] it was unclear if sample size calculations had been conducted. In one RCT[4] there were no withdrawals and all patients were included in the analyses. In two RCTs[10,11] there were withdrawals and not all patients were included in the analyses. This may introduce attrition bias in that there may be systematic differences between the patients analyzed and those that were not analyzed.

Summary of Findings

Two systematic reviews[6,9] and three RCTs[4,10,11] were identified regarding the clinical effectiveness of nociception monitoring in adult patients undergoing surgery under general anesthesia.

Relevant study findings are summarized and a table of the main study findings and authors' conclusions are presented in Appendix 4, Tables 6 and 7.

Clinical Effectiveness of Nociception monitoring

Two systematic reviews[6,9] and three RCTs[4,10,11] were identified regarding the clinical effectiveness of nociception monitoring in adult patients undergoing surgery under general anesthesia. It should be noted that there was considerable overlap in the RCTs included in the two systematic reviews (Appendix 5).

Intraoperative opioid consumption:

Results from two systematic reviews[6,9] showed that intraoperative opioid consumption was generally less with nociception monitoring compared with standard monitoring but in some of the individual studies included in these systematic reviews, the between group differences were not statistically significant.

Three RCTs[4,10,11] found that intraoperative opioid consumption was less with nociception monitoring compared with standard monitoring, and the between group difference was statistically significant in two RCTs[4,11] and not statistically significant in one RCT.[10]

Details of the opioids used are presented in Appendix 2.

Intraoperative adverse events:

Two systematic reviews[6,9] and one RCT[11] showed that intraoperative adverse events (hemodynamic events) were not statistically significantly different between nociception monitoring and standard monitoring.

Intraoperative movement:

Two systematic reviews[6,9] and one RCT[10] showed that intraoperative movement was not statistically significantly different between nociception monitoring and standard monitoring.

Postoperative opioid/analgesic use:

One systematic review[6] and one RCT[10] showed that postoperative opioid consumption was not statistically significantly different between nociception monitoring and standard monitoring. One RCT[4] showed that number of patients needing additional analgesics were greater in the control monitoring group compared to the nociception monitoring group, however the between group difference was not statistically significant.

Postoperative pain rating

Two systematic reviews[6,9] and two RCTs[4,10] showed that postoperative pain rating was not statistically significantly different between nociception monitoring and standard monitoring.

Postoperative adverse events:

One systematic reviews[9] and one RCTs[10] showed that postoperative adverse events (nausea and vomiting) was not statistically significantly different between nociception monitoring and standard monitoring.

In summary, the results suggest that intraoperative opioid consumption may be less with nociception monitoring compared to standard monitoring, however between group differences were not always statistically significant. There appeared to be no statistically significant differences between nociception monitoring and standard monitoring with respect to intraoperative adverse events, postoperative opioid or analgesic consumption, postoperative pain, and postoperative adverse events.

Cost-Effectiveness

No relevant evidence regarding the cost-effectiveness of nociceptive monitoring in adult patients undergoing surgery under general anesthesia was identified; therefore, no summary can be provided

Guidelines

No evidence-based guideline on nociceptive monitoring in adult patients undergoing surgery under general anesthesia was identified; therefore, no summary can be provided.

Limitations

There was considerable overlap in the studies (Appendix 5) included in the two systematic reviews hence the findings are not exclusive.

As both systematic reviews included one RCT involving children, summary estimate results from meta-analyses were presented only if the RCT involving children was not included, otherwise the results of each individual study were presented separately. Furthermore, the studies were heterogeneous, a limitation also mentioned in the included systematic reviews.[6,9]

Types of outcomes that were reported, varied across studies; not all the same outcome types were reported in all the studies.

Details of standard monitoring were not presented. Hence it was unclear if the standard monitoring procedure varied across studies. Additionally, the types of surgery varied across the studies, hence comparing postoperative outcomes across the different studies may not be ideal. Variability in the types of surgeries was also mentioned as a limitation in the included systematic reviews.[6,9]

None of the studies indicated what would be considered a clinically important difference, hence it was difficult to know if the differences observed in the studies were clinically relevant.

None of the studies were conducted in Canada. The included studies, were conducted in Europe and Asia, where anesthetic and surgical protocols may differ, hence the findings may not be generalizable to the Canadian setting.

No relevant cost-effectiveness studies or evidence-based guidelines on nociceptive monitoring in adult patients undergoing surgery under general anesthesia were identified

Conclusions and Implications for Decision or Policy Making

Two systematic reviews[6,9] and three RCTs[4,10,11] were identified regarding the clinical effectiveness of nociception monitoring in adult patients undergoing surgery under general anesthesia. No relevant cost-effectiveness studies or evidence-based guideline on nociceptive monitoring on pain, opioid/pain medication consumption and/or opioid-related adverse events in adult patients undergoing surgery under general anesthesia was identified

Based on the results of the included studies, there is a suggestion that intraoperative opioid consumption may be generally less with nociception monitoring compared with standard monitoring, however the between group differences were not always statistically significant. There appeared to be no statistically significant difference between nociception monitoring and standard monitoring with respect to intraoperative adverse events, postoperative opioid or analgesic consumption, postoperative pain, and postoperative adverse events.

The findings need to be interpreted in the light of limitations (such as considerable overlap in the studies included in the two systematic reviews, heterogeneity among the studies, varied types of surgery, varied settings, lack of information available on standard monitoring, and not all relevant outcomes reported in all the included studies). Additional studies on nociception monitoring for each individual surgery type, and anesthetic protocols would provide a better understanding of the extent to which nociception monitoring affects outcomes in specific circumstances. Studies are also needed to investigate the cost-effectiveness of the various nociception monitoring systems to assess the feasibility of such monitoring.

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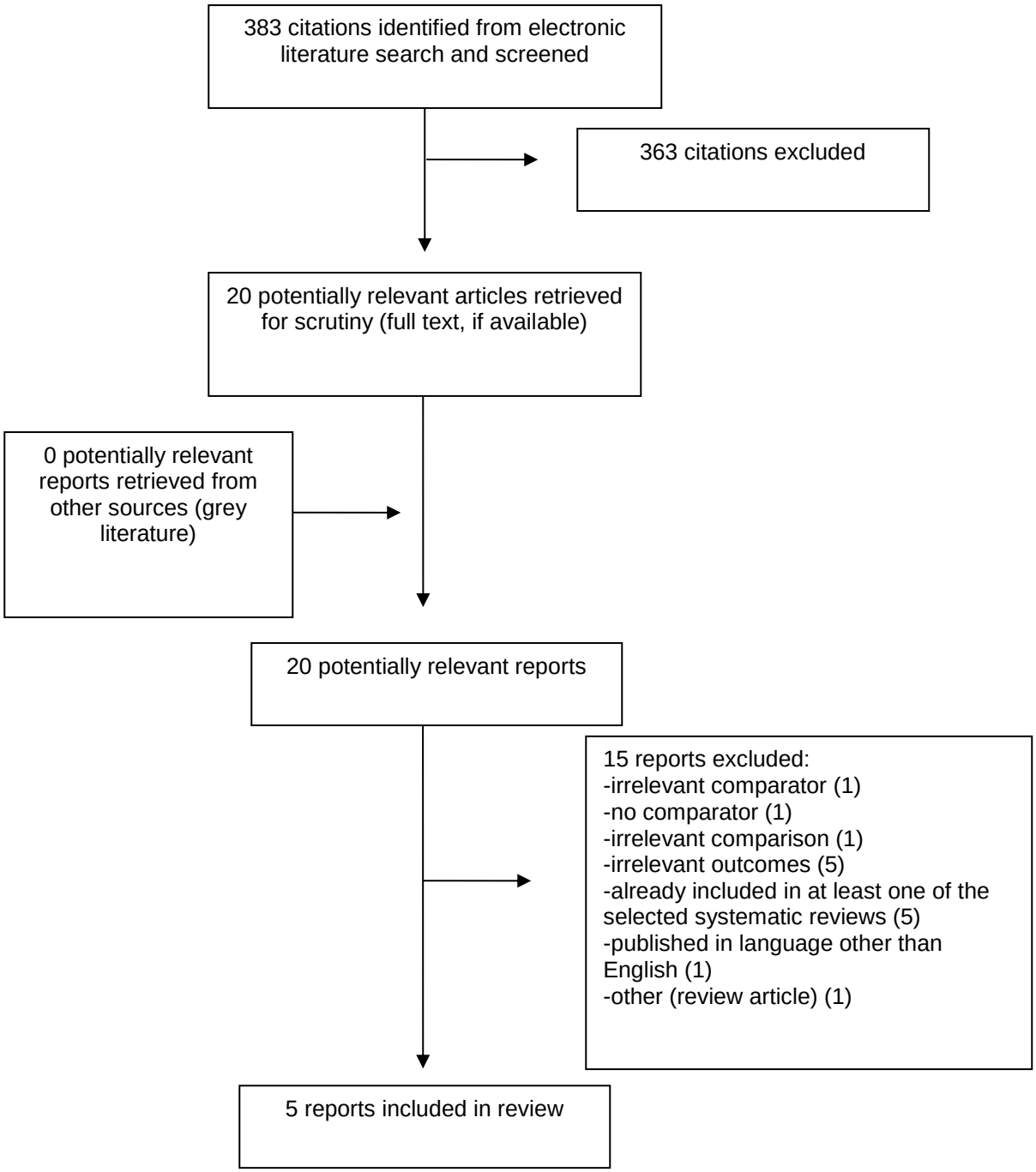
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Won,[9] 2018, South Korea	Systematic review including 6 RCTs published between 2010 and 2016. Three of the RCTs were conducted in Germany, 1 RCT was conducted in Italy, and 2 RCTs were conducted in South Korea. Inclusion criteria: "(1) studies involving patients who underwent general anesthesia during surgery, (2) studies comparing the surgical stress index or SPI-guided analgesia and conventional analgesia (standard clinical practice), and (3) studies involving assessment of the intraoperative opioid requirement and degree of postoperative pain as evaluated with the numerical rating scale (NRS) for pain, extubation time, and adverse events including hemodynamic or somatic events or PONV as the main outcomes." p. 4388-4389. Exclusion criteria: NR	Patients undergoing elective surgery (5 RCTs on adults and 1 RCT on children). Types of surgery: thyroidectomy, orthopedic procedures, gynecological procedures, cholecystectomy, throat surgery, adenotonsillectomy N = 418 adults (in 5 RCTs) + 45 children (in 1 RCT) Age (range) (years): 18 to 70 (in 5 RCTs), and 3 to 10 in 1 RCT % Female: 31% to 82% in the 5 adult RCTs and 49% in the RCT with children. ASA class: ASA 1 and ASA II	SPI guided procedure versus conventional procedure (Opioid/ anesthetic agent used in adult RCTs: remifentanil/ propofol in 3 RCTs, oxycodone/ sevoflurane in I RCT, and sufentanil/ sevoflurane in 1 RCT. Opioid/ anesthetic agent used in the RCT on children: fentanyl/ sevoflurane)	Intraoperative opioid consumption; extubation time; postoperative pain severity (NRS score); perioperative adverse events Follow up: intraoperative and post-operative (24h)
Gruenewald,[6] 2017, Germany	Systematic review including 7 RCTs published between 2010 and 2015. Inclusion criteria: "Population included patients (adults or children) who received general anesthesia including opioid analgesia. The intervention was guidance of opioids performed by usage of analgesia/nociception monitoring in comparison to a control group, where no additional monitoring was used to monitor analgesia/nociception (only clinical judgement, *i.e.*	Patients undergoing surgery (6 RCTs on adults and 1 RCT on children). Types of surgery/procedure: Orthopedic procedures, gynecological procedures, cholecystectomy, ENT, colonoscopy, gastroscopy surgery, adenotonsillectomy N = 638 adults (in 6 RCTs) + 45 children (in 1 RCT	Monitoring devices (ANI, CARDEAN, and SPI) used versus standard of care (Opioid/ hypnotic agent used in adult RCTs: remifentanil/ propofol in 3 RCTs, al fentanil/ propofol in I RCT, [fentanyl and morphine]/ [sevofluranr or desflurane or propofol], and sufentanil/ sevoflurane in 1 RCT. Opioid/ hypnotic agent	Intraoperative opioid consumption; intraoperative movement; intraoperative hypertension and/ or tachycardia; intraoperative hypotension and/or bradycardia; time to emergence; postoperative pain; postoperative opioid consumption. Follow up: intraoperative and post-operative

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	treatment as usual).” p.203-204. Exclusion criteria: NR	Age (years): NR % Female: NR ASA class: ASA I and ASA II; except in one study ASAI, ASA II, and ASA III	used in the RCT on children: fentanyl/ sevoflurane and nitrous oxide])	

ANI = Analgesia Nociception Index; ASA = American Society of Anesthesiologists; CARDEAN = Cardiovascular Depth of Analgesia; NR = not reported; NRS = numerical rating scale; PONV = post-operative nausea and vomiting; RCT = randomized controlled trial; SPI = Surgical Pleth Index

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Dundar[4] 2018, Turkey	RCT (no mention of blinding), single center. Inclusion criteria: “ASA I-II female patients aged between 18 and 65 years who underwent elective breast surgery in our clinic” p.482 Exclusion criteria: “We excluded patients with cardiac arrhythmia, central or autonomous nervous system disorders and on opioid treatment, infections at the site of planned blockade, and known local anesthetic allergy.” p. 482	Adults undergoing elective breast surgery N = 44 (22 in ANI group and 22 in control group) Age (mean ± SD) (years): 49.09 ± 11.59 in ANI, 46.55 ± 8.18 in control. Weight (kg) (mean ± SD): 71.23 ± 10.69, 70.14 ± 11.13 % Female: 100% ASA class: NR	ANI versus control (managed conventionally according to hemodynamic parameters) (Induction of anesthesia was with fentanyl, propofol, and rocuronium bromide. Patients received thoracic paravertebral block for perioperative analgesia before undergoing surgery under general anesthesia.)	Intraoperative remifentanil consumption, duration of postoperative recovery room stay, pain rating during recovery room stay, additional analgesic requirement
Upton[10] 2017, Australia	RCT, single blind, single center. The anesthesiologist was aware of the group allocation but the patient, surgical staff, and recovery room staff were unaware of group allocation. Inclusion criteria: “Patients were 18 to 75 years old, with an American Society of Anesthesiologists Physical Status score of 1 to 2 and a body mass index range of	Adults undergoing lumbar discectomy or laminectomy N = 54 randomized and 50 included in the analysis (24 in ANI group and 26 in control group) For the 50 patients analyzed: Age (mean [range]) (years): 47 (21 to 75) in ANI, and 51 (20 to 75)	ANI versus control (anesthesiologist’s standard clinical practice) Induction of anesthesia was with fentanyl, and propofol; and followed by rocuronium for muscle relaxation	Outcomes in the recovery room: pain rating (primary outcome); duration of stay; total fentanyl administration in adverse events Outcomes in the intraoperative phase: total fentanyl administration; incidence of movement

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	18.5 to 35 kg/m^2." p.82 Exclusion criteria: "Patients with nonregular sinus cardiac rhythm, implanted pacemakers, prescribed antimuscarinic agents, α2-adrenergic agonists, β1-adrenergic antagonists, and antiarrhythmic agents were excluded, as these factors may make ANI scores unreliable. Patients with preoperative opioid use equivalent to >20 mg oxycodone daily for >6 weeks, intolerance to trial medication, intraoperative cardiac arrhythmia, and surgery lasting >3 hours were also excluded." p. 82	in control Weight (kg) (mean ± SD): 85 ± 25 in ANI, 82 ± 15 in control % Female: 54% ASA class: ASA I and ASA II		
Wu[11] 2016, China	RCT, single blind, single center. Inclusion criteria: "(1) American Society of Anesthesiologists (ASA) class I or II; (2) age 18–65 years old; and (3) body mass index (BMI) 18–30 kg/m^2." p. 2 of 7 Exclusion criteria: "(1) pregnancy; (2) allergy to the agents used in the study; (3) hypertension; (4) hypotension; (5) tachycardia; or (6) bradycardia." p. 2 of 7	Adults undergoing elective unilateral modified mastectomy under total intravenous anesthesia N = 120 randomized, 114 received allocated intervention and 107 (54 in monitored group and 53 in control group) were included in the analysis. For the 107 analyzed: Age (mean ± SD) (years): 47 ± 7 in monitored group, and 48 ± 8 in control group. Weight (kg) (mean ± SD): 63 ± 9 in monitored, 63 ± 8 in control. % Female: 100% ASA class: NR	IoC (IoC1 and IoC2) monitoring versus control (i.e. not monitored for depth of anesthesia). Anesthesia with propofol, fentanyl, and cistracurium. IoC1 is indicative of sedative depth, and was used as guide for adjusting propofol target concentration. IoC2 is indicative of analgesic depth, and was used as guide for adjusting remifentanil target concentration.	Use of remifentanil, use of propofol, and quality of anesthetic recovery. Intraoperative adverse events (hypertension, hypotension, tachycardia, bradycardia, body movements, intraoperative awareness).

ANI = Analgesic Nociception Index; ASA = American Society of Anesthesiologists; IoC = index of consciousness; RCT = randomized controlled trial; SD = standard deviation;

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[7]

Strengths	Limitations
Won,[9] 2018, South Korea	
• The objective was clearly stated • Multiple databases (MEDLINE, EMBASE, Cochrane Controlled Trials register, Cochrane database of systematic reviews, web if Science, and Scopus) were searched until February 2017 • Inclusion criteria was stated • Study selection was described and a flow chart was presented • A list of included studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers. • Quality assessment was done independently by two reviewers, using the Cochrane risk of bias tool. Majority of the included studies were of good quality • Characteristics of the individual studies were presented • Meta-analysis was conducted • The authors mentioned that there were no conflicts of interest	• Exclusion criteria was not explicitly stated • A list of excluded studies was not provided • Publication bias was not explored as it was not considered feasible with the small number of studies (< 10 studies)
Gruenewald,[6] 2017, Germany	
• The objective was clearly stated • A single databases (PubMed) was searched until April 2016 2017 • Inclusion criteria was stated • Study selection was described and a flow chart was presented • A list of included studies was provided • Quality assessment was done using the Jadad score (score ranged between 2 and 3, with majority of the studies (5 of 7, i.e. 70%) having score 3. Jadad score range is 0 (poor quality) to 5 (high quality). • Characteristics of the individual studies were presented but lacked details • Meta-analysis was conducted • Conflicts of interest were reported	• Exclusion criteria was not explicitly stated • Unclear if article selection was done in duplicate • Unclear if data extraction was done in duplicate • Unclear if quality assessment was conducted in duplicate • A list of excluded studies was not provided • The authors mentioned that there could be possibility of publication bias • Conflicts of interest were reported and one of the authors was associated with the manufacturer

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black checklist[8]

Strengths	Limitations
Randomized controlled trials	
Dundar,[4] 2018, Turkey	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were	• There was no mention of blinding • Details of power and sample size determinations were not presented

Strengths	Limitations
described. • Randomized using the sealed envelope method • It was mentioned that the power of the study was 89.9 but details were not presented • All patients were included in the analysis • *P* values were reported • The authors mentioned that there were no conflicts of interest	
Upton,[10] 2017, Australia	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized by computer generated numbers • Single blinded (The anesthesiologist was aware of the group allocation but the patient, surgical staff, and recovery room staff were unaware of group allocation.) • Sample size determinations were mentioned and the required sample size was achieved (25 patients were required in each group, and there were 26 in ANI and 28 in control) • Discontinuation and the associated reason were reported; 4 patients (2 in each group; 8% in ANI and 7% in control) were excluded intraoperatively due to arrhythmia or surgery lasting > 3 hours. • *P* values were reported • The authors mentioned that there were no conflicts of interest	• Not all patients randomized could be included in the analysis (4 of the 54 patients randomized were excluded)
Wu,[11] 2016, China	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized by computer generated random numbers • Single blinded (patients blinded) • Sample size determinations were mentioned and the required sample size was achieved (46 patients were required in each group, and there were 60 in each group) • Discontinuation and the associated reason were reported; 6 (10%) patients in monitored group and 7 (12%) patients in control group • *P* values were reported • The authors mentioned that there were no conflicts of interest	• Not all patients randomized could be included in the analysis (13 of the 120 patients randomized were excluded)

abb = abbreviation

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Won,[9] 2018, South Korea</td></tr>
<tr><td>SPI-guided analgesia compared with control (conventional analgesia) for various outcomes in adult patients undergoing surgery (note this systematic review also included one RCT on pediatric patients, hence summary estimates for outcome results which included this RCT will not be presented here, instead results (effect size) for each individual RCT on adult patients will be presented)

Intraoperative outcomes
<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>Effect measure</th><th>Effect size</th><th>Heterogeneity (I^2)</th></tr>
<tr><td>Intraoperative opioid consumption (µg/kg/minute)</td><td>5</td><td>SMD (95% CI)</td><td>-0.41 (-0.70 to -0.11</td><td>53%</td></tr>
<tr><td>Extubation time (min)</td><td>3</td><td>MD (95% CI)</td><td>-3.20 (-4.82 to -1.78);
-2.80 (-5.20 to -0.40)
-0.70 (-1.67 to 0.27);</td><td>NR</td></tr>
<tr><td>Intraoperative unwanted somatic movement</td><td>3</td><td>RR (95% CI)</td><td>0.68 (0.30 to 1.52)</td><td>72%</td></tr>
<tr><td>Intraoperative hemodynamic adverse events (hypertension)</td><td>2</td><td>RR (95% CI)</td><td>0.78 (0.55 to 1.10);
0.15 (0.08 to 0.28)</td><td>NR</td></tr>
<tr><td>Intraoperative hemodynamic adverse events (tachycardia)</td><td>2</td><td>RR (95% CI)</td><td>0.77 (0.56 to 1.07);
0.23 (0.01 to 4.74)</td><td>NR</td></tr>
</table>
Postoperative outcomes
<table>
<tr><th>Outcome</th><th>No. of RCTs</th><th>Effect measure</th><th>Effect size</th><th>Heterogeneity (I^2)</th></tr>
<tr><td>Postoperative pain score (at 24 h)</td><td>4</td><td>MD (95% CI)</td><td>-0.15 (-0.60 to 0.29)</td><td>63%</td></tr>
<tr><td>Postoperative nausea and vomiting</td><td>3</td><td>RR (95% CI)</td><td>1.32 (0.30 to 5.68);
0.86 (0.45 to 1.62);
0.64 (0.12 to 3.46)</td><td>NR</td></tr>
</table>
</td><td>The authors mentioned that "Compared with conventional analgesia, SPI-guided analgesia can reduce intraoperative opioid consumption and facilitate extubation. Moreover, no intergroup difference was observed in the degree of postoperative pain or incidence of perioperative adverse events." p. 4386</td></tr>
</table>

Main Study Findings	Authors' Conclusion
Gruenewald,[6] 2017, Germany	
Procedures using monitoring devices (SPI, ANI, and CARDEAN) compared to control (standard clinical care) for various outcomes in adult patients undergoing surgery (note this systematic review also included one RCT on pediatric patients, hence summary estimates for outcome results which included this RCT will not be presented here, instead results (effect size) for each individual RCT on adult patients will be presented)	The authors mentioned that "Monitoring analgesia/nociception is often reliant on regular physiologic conditions, like sinus rhythm. Opioid guidance dependent on analgesia/nociception monitoring during anesthesia may have beneficial and clinically relevant effects, however the number of currently available randomized controlled studies is low and conclusions are hampered by heterogeneity. More studies with focussed clinical endpoints are therefore needed." p. 200

Intraoperative outcomes

Outcome	No. of RCTs	Effect measure	Effect size	Heterogeneity (I^2)
Intraoperative opioid consumption (unit not specified)	6	SMD (95% CI)	-0.68 (-1.13 to -0.23); -0.44 (-0.76 to -0.12); -0.30 (-0.74 to 0.13); -0.19 (-0.70 to 0.32); 0.07 (-0.29 to 0.43); 0.33 (0.00 to 0.66);	NR
Intraoperative movement events	4	IRR (95% CI)	0.54 (0.29 to 1.00)	100%
Intraoperative hypertension and/or tachycardia	3	IRR (95% CI)	1.48 (0.68 to 3.24); 1.06 (0.26 to 4.22); 0.54 (0.29 to 1.00)	NR
Intraoperative hypotension and/or bradycardia	3	IRR (95% CI)	0.45 (0.13 to 1.62)	100%

Postoperative outcomes

Outcome	No. of RCTs	Effect measure	Effect size	Heterogeneity (I^2)
Time to emergence from anesthesia	4	SMD (95% CI)	-0.82 (-1.15 to -0.49); -0.39 (-0.83 to 0.05); -0.14 (-0.58 to 0.29); 0.28 (-0.08 to 0.64)	NR
Postoperative pain rating (with imputation using	5	SMD (95% CI)	-0.14 (-0.64 to 0.37); -0.04 (-0.48 to	NR

Main Study Findings					Authors' Conclusion
median value for mean when median was reported instead of mean and also imputing SD values)			0.39); 0.00 (-0.43 to 0.44); 0.05 (-0.27 to 0.37); 0.15 (-0.21 to 0.51)		
Postoperative pain rating (no imputation)	4	SMD (95% CI)	0.04 (-0.15 to 0.24)	100%	
Postoperative opioid administration	2	SMD (95% CI)	-0.07 (-0.50 to 0.4); 0.12 (-0.24 to 0.5)	NR	

ANI = analgesia nociception index; CARDEAN = Cardiovascular Depth of Analgesia; CI = confidence interval; IRR = incidence rate ratio; MD = mean difference; NR = not reported; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; SMD = standardized mean difference; SPI = Surgical Pleth Index.

Table 7: Summary of Findings of Included Primary Clinical Studies

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Randomized controlled study</td></tr>
<tr><td colspan="2">Dundar,[4] 2018, Turkey</td></tr>
<tr><td>Comparison of ANI monitoring with control (conventional method based on hemodynamic parameters) in adult women undergoing elective breast surgery (N = 44)

<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Effect size, mean ± SD</th><th rowspan="2">P value</th></tr>
<tr><th>ANI</th><th>Control</th></tr>
<tr><td>Intraoperative remifentanil consumption (µg)</td><td>630 ± 422</td><td>965 ± 544</td><td>0.027</td></tr>
<tr><td>Duration of stay in postoperative RRm (min)</td><td>43 ± 12</td><td>44 ± 11</td><td>0.844</td></tr>
<tr><td>VAS scores during stay at RRm</td><td>NR</td><td>NR</td><td>0.676</td></tr>
<tr><td>No of patients with additional analgesic requirement</td><td>1</td><td>4</td><td>>0.05</td></tr>
</table>
</td><td>The authors mentioned that "In patients under general anesthesia ANI monitorisation can help optimisation of opioid consumption and provide data about nociception/ antinociception intraoperatively but further experimental and clinical trials in a large scale are needed." p. 481</td></tr>
<tr><td colspan="2">Upton,[10] 2017, Australia</td></tr>
<tr><td>Comparison of ANI monitoring with control (based on standard clinical practice) in adults undergoing lumbar discectomy and laminectomy (N = 50)

<u>Comparison of outcomes during the intraoperative phase</u>

Emergence time (from final suture to awake time) (min), (mean ± SD) was 14 ± 6 in the ANI group, and 15 ± 6 in the control group, P > 0.99.

Total intraoperative fentanyl administration (µg), (mean ± SD) was 416 ± 191, and 426 ± 247 for control group; P >0.99.

Intraoperative movement was 17% in ANI group, and 19% in the control group; P >0.99.</td><td>The authors mentioned that "Patients receiving intraoperative ANI-guided fentanyl administration during sevoflurane anesthesia for lumbar discectomy and laminectomy demonstrated decreased pain in the recovery room, likely as a result of more objective intraoperative fentanyl administration." p. 81</td></tr>
</table>

Main Study Findings	Authors' Conclusion
Comparison of outcomes during stay in the recovery room (RRm): NRS pain score (during 0 to 90 mins in the RRm), was on average 1.3 units lower in the ANI group compared to the control group with 95% CI of -0.4 to 2.4; *P* = 0.01. NRS pain score (during 15 to 55 mins in the RRm), was on average 1.8 units lower in the ANI group compared to the control group with 95% CI of -0.8 to 2.7; *P* =0.007. Time spent in the RRm, (min), (mean ± SD) for ANI group was 97 ± 36, and for control group was 100 ± 22; *P* > 0.99. Total fentanyl administration in the RRm, was 64% lower in the ANI group compared to the control group, with 95% CI of -12% to 85%; *P* = 0.44. Total fentanyl administration in the RRm (µg), (mean ± SD) was 135 ± 180, and 248 ± 200 for control group; *P* = 0.44 Fentanyl administration rate (bolus per hour), for ANI group is 1.3 ± 1.4, and for control group was 2.6 ± 1.6, *P* = 0.004. Naloxone requirement was 0% in ANI group and 4% in control group; *P* >0.99. Worst nausea (based on NRS [0 to 10]), (mean ± SD) for ANI group was 1 ± 2, and for control group was 2 ± 3; *P* = 0.43. Emetic episodes were 0% in ANI group, and 8% in the control group; *P* >0.99. Antiemetic requirement was17% for ANI group, and 35% for control group; *P* >0.99. Postoperative shivering was 4% in the ANI group, and 35% in the control group; *P* =0.80. Airway intervention requirement was 13% in ANI group, and 4% in the control group; *P* >0.99.	
Wu,[11] 2016, China	
Comparison of IoC (IoC1 and IoC2) monitored group with control group (based on vital signs such as blood pressure and heart rate) in adults undergoing modified radical mastectomy (N = 107) **Comparison of outcomes during the intraoperative phase** *Use of remifentanil:* Adjustment frequency of target concentration (times/ surgery) was 2.9 ± 1.9 for monitored group, and 2.0 ± 0.2 for control group; *P* =0.009. Infusion duration (h) 1.1 ± 0.6 for monitored group, and 1.3 ± 0.7 0.428 for control group; *P* = 0.428 Mean dose (µg/kg/ h) 3.8 ± 1.9 for monitored group, and 3.2 ± 1.2 for control group; *P* =0.003 *Use of propofol*: Adjustment frequency of target concentration (times/surgery) 3.0 ± 2.0 for monitored group, and 3.0 ± 1.9 for control group; *P* = 0.444	The authors mentioned that "In summary, EEG anesthesia depth index (IoC) monitoring during TIVA is safe and effective for patients with breast cancer. IoC1-targeted propofol dosing does not seem to be significantly different to hemodynamic-based monitoring, whereas the application of IoC2 might be used to guide the use of remifentanil. It might reduce the occurrence of adverse events and keep hemodynamics more stable, but its reliability in predicting body movements as well as the anti-interference ability should be further improved." p. 6 of 7

Main Study Findings	Authors' Conclusion
Infusion duration (h) 1.6 ± 0.5 for monitored group, and 1.9 ± 0.6 for control group; *P* = 0.523 Mean dosage (µg kg-1 h-1) 8.8 ± 1.1 for monitored group, and 8.3 ± 1.0 for control group; *P* = 0.903 *Quality of anesthetic recovery*: Voluntary eye opening (min) 5.4 ± 3.1 for monitored group, and 6.2 ± 2.3 for control group; *P* = 0.782 Extubation time (min) 9.8 ± 6.1 for monitored group, and 9.3 ± 5.7 for control group; *P* = 0.816 Awakening score 3.9 ± 0.7 for monitored group, and 4.0 ± 0.9 for control group; *P* = 0.960 *Intraoperative adverse events frequency:* Hypertension events were 5 (9 %) for monitored group, and 9 (17 %) for control group; *P* = 0.236 Hypotension events were 6 (11 %) for monitored group, and 11 (21 %) and for control group; *P* = 0.173 Tachycardia events were 0 for monitored group, and 2 (4 %) for control group; *P* = 0.150 Bradycardia events were 9 (17 %) for monitored group, and 4 (8 %) for control group; *P* = 0.149 Body movements were in 6 (11 %) for monitored group, and 10 (19 %) for control group; *P* = 0.261 Intraoperative awareness events were 0 for monitored group, and 0 for control group; *P* = 1.000 Total adverse events were in 26 (48 %) for monitored group, and 36 (68 %) for control group; *P* = 0.038 Number of patients with adverse events was 19 (35 %) for monitored group, and 25 (47 %) for control group; *P* = 0.208	

ANI = analgesia nociception index; CI = confidence interval; EEG = electroencephalogram; IoC = index of consciousness (IoC1 indicative of sedative depth and IoC2 indicative of analgesic depth); NR = not reported; NRS = numerical rating scale; RR = risk ratio; RRm = recovery room; SD = standard deviation; TIVA = total intravenous anesthesia; VAS = visual analog scale

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Won, 2018[9]	Gruenefeld, 2017[6]
Won, 2016	x	
Colombo, 2015	x	x
Park, 2015[a]	x	x
Szental, 2015		x
Gruenewald, 2014	x	x
Bergmann, 2013	x	x
Chen, 2010	x	x
Martinez, 2010		x

[a] RCT involved children. All other RCTs involved adults