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Preservation versus dissection of the intercostobrachial nerve for breast cancer surgeries: a systematic review and meta-analysis

Nada M. Al-dardery, MBBCh[a], Abdulrhman M. Khaity, MBBCh[b,*], Khaled A. Albakri, MBBCh[c], Ahmed T. Abdelsattar, MBBCh[a], Amira Y. Benmelouka, MD[d], Theodore Lee, MD[e], Jose A. Foppiani, MD[f,g], Samuel J. Lin, MD, MBA[g]

Introduction: This meta-analysis aimed to compare the efficacy of preservation of the intercostobrachial nerve (ICBN) versus its dissection for patients who underwent breast surgery.

Methods: The authors searched Web of Science, PubMed, Cochrane CENTRAL, and Scopus from inception until March 2023. Records were screened for eligible studies, and all relevant outcomes were pooled as an odds ratio (OR) with the corresponding 95% CI in the meta-analysis models using RevMan version 5.4.

Results: These results from 11 studies (1021 patients) favored preservation of the ICBN over its dissection in terms of anaesthesia and hypaesthesia [OR 0.50, (95% CI, 0.31–0.82); $P = 0.006$] and [OR 0.33, (95% CI, 0.16–0.68); $P = 0.003$], respectively. Whereas the overall effect favored ICBN dissection over preservation in the case of hyperaesthesia [OR 4.34, (95% CI, 1.43–13.15); $P = 0.01$]. Conversely, no significant variance was detected between the two groups in terms of pain [OR 0.68, (95% CI, 0.28–1.61) $P = 0.38$], paraesthesia [OR 0.88, (95% CI, 0.49–1.60); $P = 0.68$], and analgesia [OR 1.46, (95% CI, 0.05–45.69); $P = 0.83$].

Conclusion: This meta-analysis revealed that the preservation of the ICBN has a significant effect on the disturbance of sensory parameters of hypaesthesia and anaesthesia when compared to its dissection. Further studies with larger sample sizes are recommended to precisely compare both techniques on a wider range of parameters.

Keywords: breast cancer, dissection, intercostobrachial nerve, post-mastectomy pain syndrome, preservation

Introduction

Breast cancer is one of the worldwide most prelevant malignancies in women[1]. In 2020, it represented 11.7% of new cancer cases and caused 685 000 deaths[2,3]. Breast cancer management is complex and requires an interdisciplinary approach. Although several advancements in the therapeutic approach for breast carcinoma have occurred, surgery remains one of the most effective procedures for treating breast tumours[4]. However, many patients who undergo mastectomy may suffer from surgically related complications. Among those complications, one of the most frequent is post-mastectomy pain syndrome (PMPS), which affects 25–60% of women who undergo surgical management for breast carcinoma[5,6].

Generally, PMPS is characterized by chronic persistent pain, which can be burning, aching, or dull in nature. It can afflict the anterior side of the axilla, chest, and/or upper arm. In its worst form, it may cause permanent loss of sensation in the area supplied by the intercostobrachial nerve (ICBN)[5,7]. The fundamental risk elements for the prognosis of PMPS are hypothesized

HIGHLIGHTS

- Breast cancer surgeries often involve the removal of lymph nodes from the axilla, which can result in damage to the intercostobrachial nerve (ICBN).
- Preservation involves leaving the nerve intact, while dissection involves removing it along with the lymph nodes.
- Our meta-analysis reveals that preservation of the ICBN through axillary lymph node dissection, when compared to its dissection, appeared to decrease the risk of some sensory disturbance parameters.
- The future of preservation versus dissection of the ICBN will depend on a variety of factors, including patient preferences, surgeon expertise, and advances in surgical technology.

[a]Faculty of Medicine, Fayoum University, Fayoum, Egypt, [b]Faculty of Medicine, Elrazi University, Khartoum, Sudan, [c]Faculty of Medicine, The Hashemite University, Zarqa, Jordan, [d]Faculty of Medicine, University of Algiers, Algiers, Algeria, [e]Georgetown University, Washington DC, [f]1st Faculty of Medicine, Charles University, Prague, Czech Republic and [g]Division of Plastic and Reconstructive Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

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*Corresponding author. Address: Faculty of Medicine, Elrazi University, Khartoum, Sudan; Tel.: +249 099 925 5031. fax: +249 0 999255031.
E-mail: abdulrhman.marwan.khaity@gmail.com (A. M. Khaity).

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to be dependent on age, BMI, and the surgical techniques used on the patient[8]. Moreover, the postulated cause of PMPS is an injury of the ICBN during quadrantectomy, mastectomy, and/or radiation therapy[3]. Additionally, anatomical proximity between the axillary lymph nodes and the ICBN often results in damage to the latter during an axillary lymph node dissection (ALND)[9]. The incidence rate of ICBN damage during the ALND procedure ranges from 80 to 100%[3]. Therefore, the risk of PMPS among patients undergoing mastectomy with ALND is high[5]. Of note, Sensory deficits are common and account for around 80% of nerve injuries according to European journals. Taylor *et al.*[10]. reported that, the incidence of hypaesthesia was 71.7% compared to 37.5% in the nerve-sparing group. Torresan *et al.*[9]. revealed that the incidence of hypaesthesia was 83.3% in the nerve transection group, compared with 46.3% in the nerve transection group.

Ultimately, the conflicting findings reported in the literature on the efficacy of ICBN preservation and the lack of evidence comparing the impact of ICBN preservation vs. dissection on the neuropathic pain associated with PMPS prompted this meta-analysis, which objects to assess the efficacy of preservation of the ICBN vs. its dissection in terms of decreasing the risk of PMPS for patients who have undergone breast surgery.

Methods

The present manuscript was meticulously prepared using the latest iteration of the Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA) , Supplemental Digital Content 1, http://links.lww.com/MS9/A322, alongside the AMSTAR 2 guidelines, Supplemental Digital Content 2, http://links.lww.com/MS9/A323[11]. The methods and analysis were carried out in strict accordance with the guidelines provided in the Cochrane Handbook of Systematic Review and Meta-analysis[12]. Additionally, the study protocol was registered on PROSPERO to ensure transparency and accountability.

Search strategy

We searched for published relevant studies in the following electronic databases: PubMed, Scopus, Cochrane Library, and Web of Science from inception until March 2023 using the following query: (Mastectomy OR "Breast Cancer") AND (Pain) AND (ICBN OR "Intercostobrachial Nerve" OR "Surgical Intervention").

Eligibility criteria

Articles that fitted the following eligibility criteria were involved in this meta-analysis:

(1) Population: Studies whose participants was females of any age after breast tumour-related surgery, with preservation of intercostobrachial nerves.
(2) Intervention: Studies where the experimental group underwent ICBN preservation.
(3) Comparator: Studies where the control group underwent ICBN nerve dissection.
(4) Outcome: The main outcome is pain while other outcomes were sensory deficits such as anaesthesia, analgesia, numbness, hypaesthesia, hyperaesthesia, paraesthesia, and diminished sensation.
(5) Study design: Studies with comparative designs, whether randomized controlled trials (RCTs) or observational studies, compared the outcomes of ICBN preservation and dissection.

We excluded theses, reviews, single-arm studies, conference abstracts, case reports, case series, and studies that assessed pain after any surgery or radiation that was not specifically for breast cancer.

Selection of studies

The screening was done in two steps by two independent authors, and any disagreements were resolved by a third. The first step was to screen the title and abstract of all recorded citations for inclusion and in the second step, full-text screening was conducted for eligibility for meta-analysis.

Data extraction

Three reviewers applied a prior data extraction independently using a uniform sheet. The following data were extracted from each included trial: (1) characters of study design, (2) characters of the study population, (3) risk-of-bias domains, (4) study outcomes including: on parameters of sensory deficits such as pain, anaesthesia, analgesia, hypaesthesia, hyperaesthesia, and paraesthesia. Disagreements were solved by a fourth author.

Quality appraisal

The assessment of risk of bias was evaluated by two independent reviewers based on the Cochrane risk-of-bias assessment tool (ROB 2.0)[13] for RCTs. The Newcastle-Ottawa scale (NOS) was used for observational studies[14]. Disagreements were solved among a third co-author.

Data synthesis

Dichotomous data were pooled as odds ratio (OR) in random-effects model using Mantel–Haenszel (M-H) method. The heterogeneity of studies was examined via visual inspection of the forest plots and assessed by the Cochrane Q and I^2 tests using RevMan version 5.4. For heterogeneity testing, a P less than 0.1 and an I-square greater than 50% were considered to indicate significant heterogeneity. We run subgroup analysis according to the duration of follow-up after surgery: 2–6 weeks, 3–6 months, and 1–3 years. In addition, we run a sensitivity analysis, also identified as a "leave-one-out test", for each outcome in the meta-analysis in multiple scenarios to test the strength of the evidence and make sure that the overall effect size was not dependent on any single study.

Publication bias

To assess publication bias among the included studies, we constructed a funnel plot to present the relationship between effect size and standard error. We used the trim-and-fill method to assess evidence of publication bias during the assessment of pain parameters in nine studies.

Results

literature search and study characteristics

Our search retrieved 536 unique citations. Following the title and abstract screening, 32 studies were appropriate for the full-text screening. During the full-text evaluation, 21 articles were excluded, six of them were left out because of discrepancies in design with our study, and nine were excluded because they met neither the primary nor the secondary outcomes of this study. Moreover, we excluded six studies because they involved different interventions. Finally, 11 studies (1021 patients), six RCTs and five observational were involved in this systematic review and meta-analysis[9,15–24]. The flow of the study selection process is illustrated in the PRISMA flow diagram in Figure 1A summary of the included articles, their design, and their findings are demonstrated in Supplementary Table 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A324, while the baseline characteristics of their populations are presented in Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/MS9/A325. Data reported from the meta-analysis of outcomes parameters are shown in detail in Supplementary Table 3, Supplemental Digital Content 5, http://links.lww.com/MS9/A326.

Risk-of-bias assessment

Randomized controlled trials

Out of six randomized clinical trials, there were four studies[16–18,20] with a high overall risk of bias, one study[22] with a moderate risk of bias, and one study[9], with a low overall risk of bias, Supplementary Figure1 (A, B), Supplemental Digital Content 6, http://links.lww.com/MS9/A327.

Observational studies

Two studies[15,24] had a low overall risk of bias, while one study[23] showed a high overall risk of bias. The other two studies[19,21] revealed a moderate overall risk of bias. More details can be seen in Supplementary Table 4, Supplemental Digital Content 7, http://links.lww.com/MS9/A328.

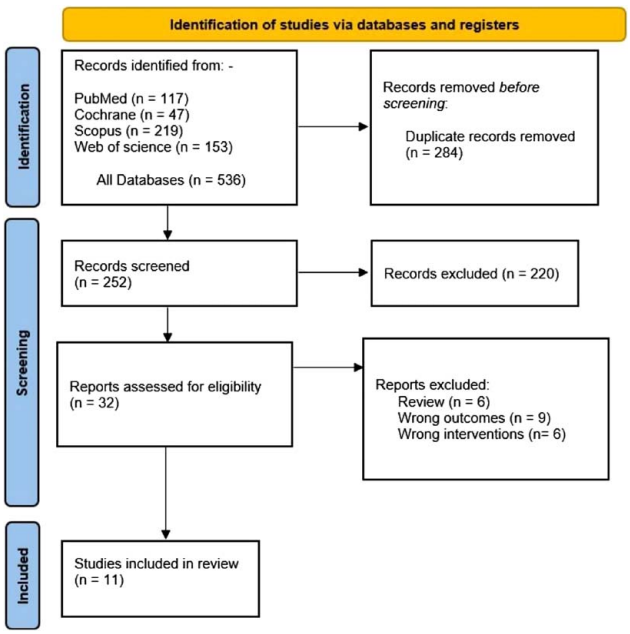

Figure 1. PRISMA flow diagram of studies' screening and selection.

Efficacy of ICBN preservation vs. its dissection on pain

The pooled effect estimates of nine studies[15–23] showed no significant difference in the efficacy of ICBN preservation or dissection on pain [OR 0.68, (95% CI, 0.28–1.61) $P = 0.38$]; Figure 2A. Significant heterogeneity was reported among the included studies (I^2 of 73%; $P = 0.0003$). The presented heterogeneity among nine studies was best resolved by excluding Taira and colleagues from the pooled study data (I^2 of 43%; $P = 0.09$).

Following correction of heterogeneity, a significant association was found between ICBN preservation and pain [OR 0.47, (95% CI, 0.24–0.89) $P = 0.02$]; Figure 2B Subgroup analysis examining the duration of follow-up after surgery revealed no significant association between ICBN preservation or dissection and pain as illustrated in Supplementary Table 5, Supplemental Digital Content 8, http://links.lww.com/MS9/A329, Figure 2C.

Publication bias

Visual inspections of trim-and-fill funnel plots in terms of pain in the overall period and subgroup analysis revealed asymmetry. Therefore, there was evidence of potential publication bias (Supplementary Figures 2, Supplemental Digital Content 9, http://links.lww.com/MS9/A330; 3, Supplemental Digital Content 10, http://links.lww.com/MS9/A331).

Efficacy of ICBN preservation vs. its dissection on other sensory parameters

Anaesthesia

The overall effect favored the preservation of ICBN over its dissection [OR 0.50, (95% CI, 0.31–0.82); $P = 0.006$; Figure 3A].

Hypaesthesia

Analysis of the pooled studies revealed significant efficacy of ICBN preservation over dissection on hypaesthesia [OR 0.33, (95% CI, 0.16–0.68); $P = 0.003$; Figure 3B]. The pooled studies showed some heterogeneity (I^2 of 64%; $P = 0.02$), which was best resolved through excluding Ka *et al.*[23]. (I^2 of 0%; $P = 0.44$). Following correction of heterogeneity, the pooled studies still favored ICBN preservation over dissection [OR 0.47, (95% CI, 0.30–0.73); $P = 0.0008$; Figure 3C].

Hyperaesthesia

The overall effect favored ICBN dissection over preservation in terms of hyperaesthesia [OR 4.34, (95% CI, 1.43–13.15); P = of 0.01; Figure 4A].

Paraesthesia

The pooled studies revealed no significant association between paraesthesia and ICBN preservation or dissection [OR 0.88, (95% CI, 0.49–1.60); $P = 0.68$; Figure 4B].

Analgesia

The pooled effect estimate did not favour either preservation or dissection of ICBN regarding analgesia [OR 1.46, (95% CI, 0.05–45.69); $P = 0.83$; Figure 4C].

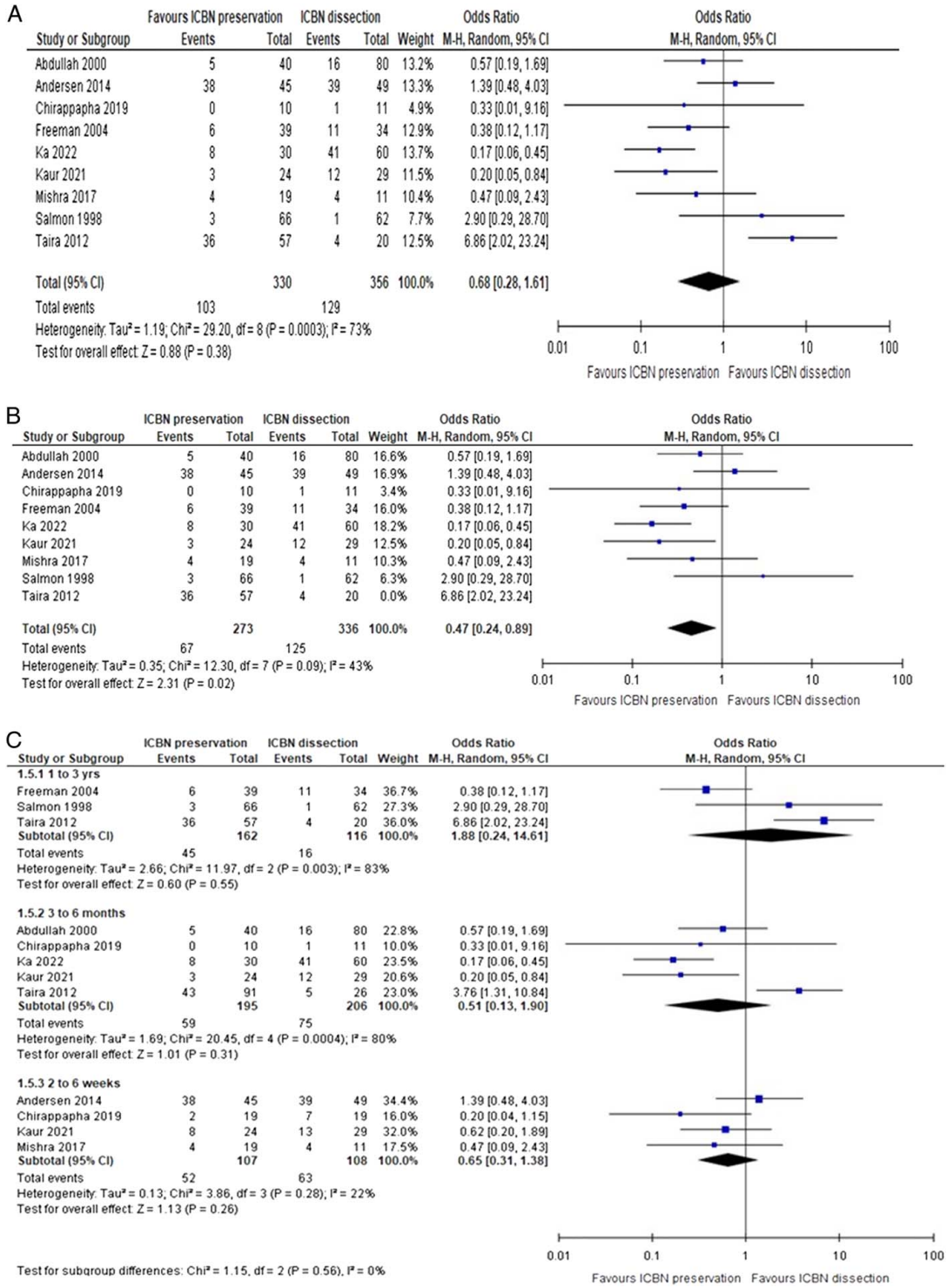

Figure 2. Forest plots of odds ratio in pain. (A) Overall pain; (B) overall pain after sensitivity analysis; (C) subgroup analysis. ICBN, intercostobrachial nerve.

Numbness

The overall effect did not favour either ICBN preservation or dissection regarding numbness [OR 0.52, (95% CI, 0.25–1.06); $P = 0.07$; Figure 5A]. Some heterogeneity was observed among the pooled studies (I^2 of 50%; $P = 0.09$), which was best solved by a sensitivity analysis test through the exclusion of Ka *et al.*[23]. (I^2 of 0%; $P = 0.80$). Following heterogeneity correction, the pooled effect estimates were still insignificant [OR 0.72, (95% CI, 0.43–1.19); $P = 0.20$; Figure 5B].

Diminished sensation

No significant association was observed between ICBN preservation or dissection and diminished sensation [OR 0.70, (95% CI, 0.40–1.23); $P = 0.22$; Figure 6].

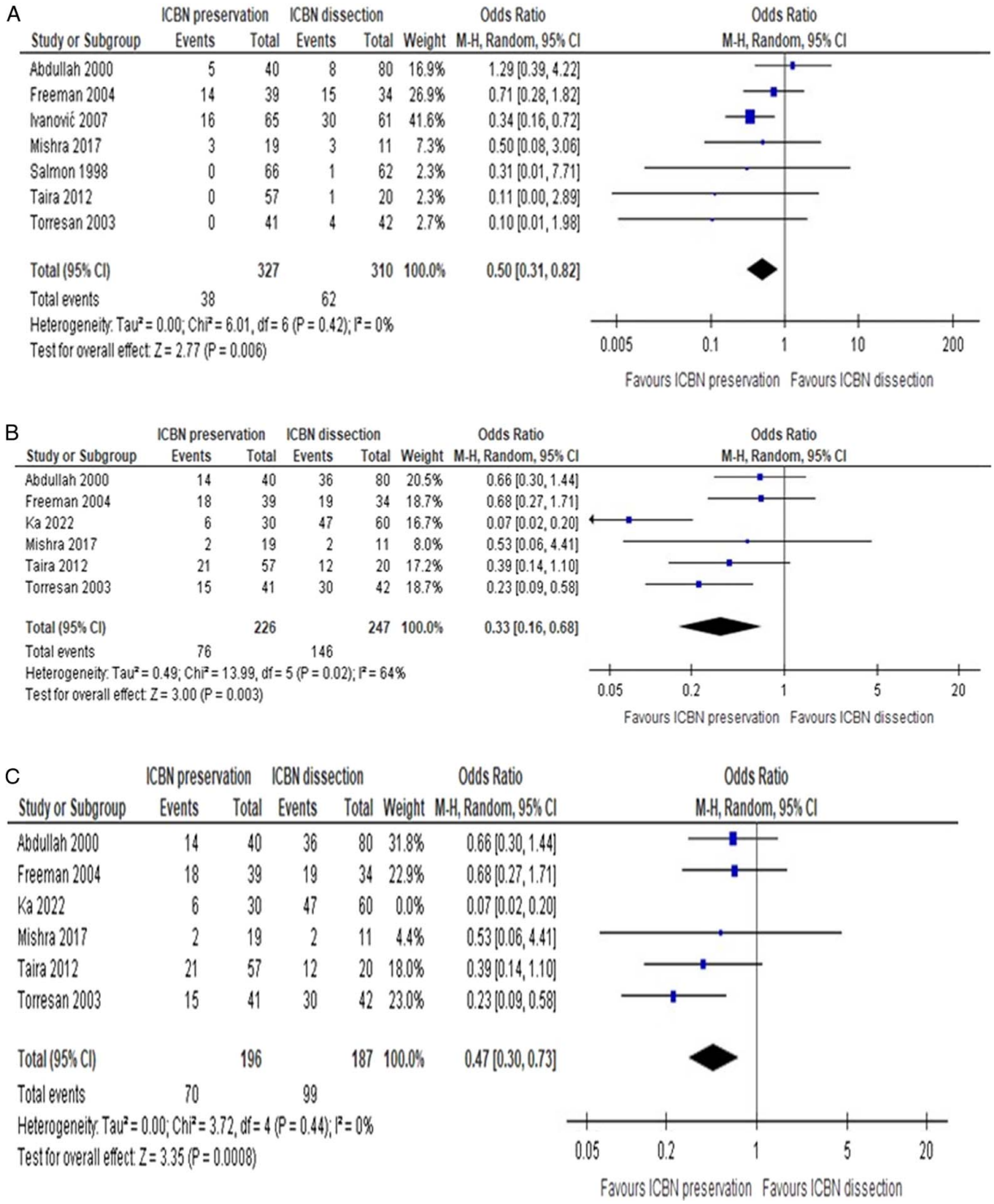

Figure 3. Forest plots of odds ratio. (A) Anaesthesia; (B) hypaesthesia; (C) hypaesthesia after sensitivity analysis. ICBN, intercostobrachial nerve.

Discussion

The findings of the present study indicate that ICBN preservation improves anaesthesia and hypaesthesia consequences after ALND but has no significant effects on pain, paraesthesia, analgesia, numbness, and diminished sensation. Additionally, ICBN dissection seems to have a significant effect on paraesthesia.

Generally, Warrier *et al.*[25]. run a meta-analysis to investigate the best management of ICBN injury during axillary dissection. They reported that the ICBN preservation during axillary dissection was associated with less sensory deficit than the division of the nerve. Sensory impairment can manifest as a little area of numbness in the axilla. That sensory disturbance is categorized

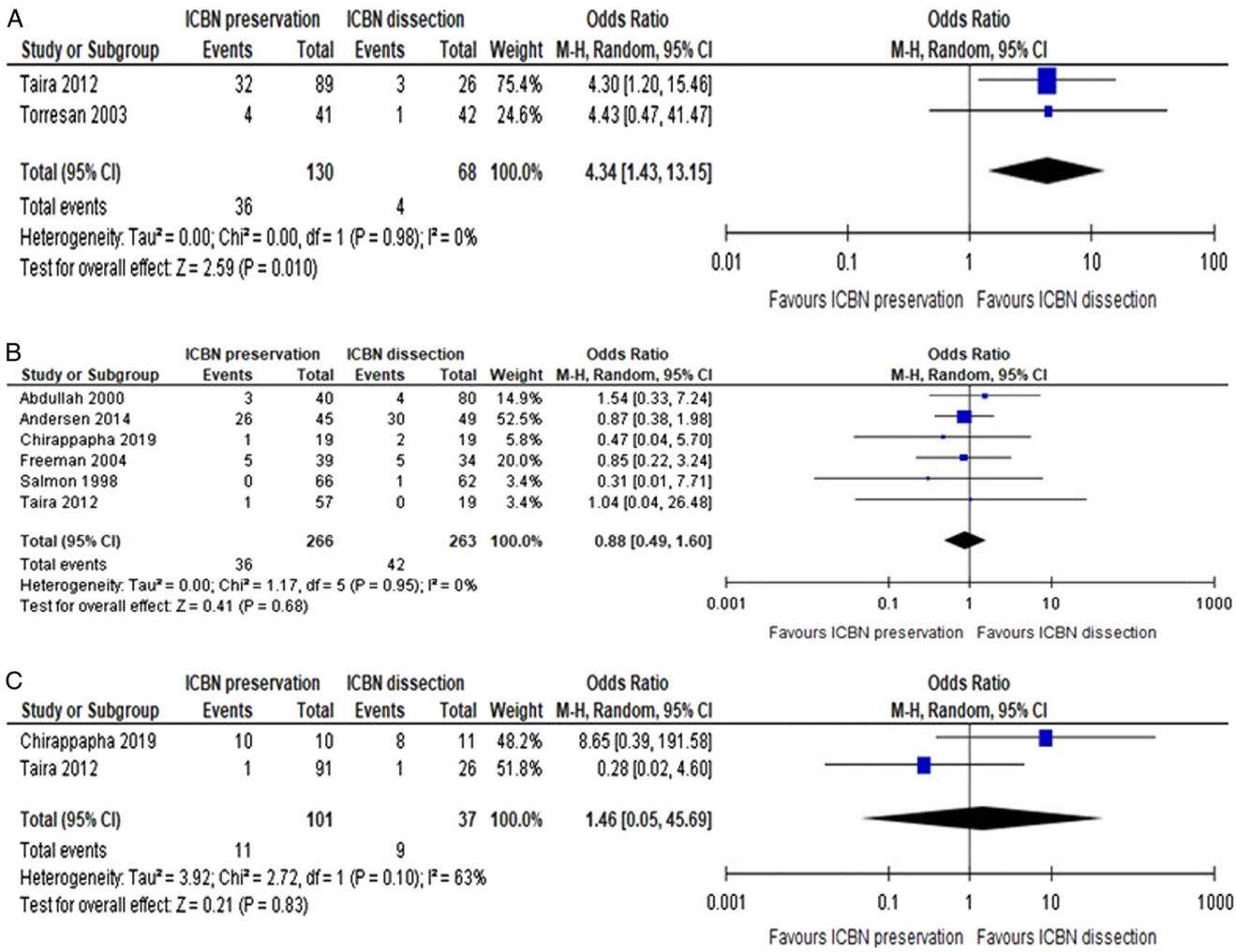

Figure 4. Forest plots of odds ratio. (A) Hyperaesthesia; (B) paraesthesia; (C) analgesia. ICBN, intercostobrachial nerve.

into two types: hypersensitivity, which is an irritable sensation due to increased activation (such as dysesthesia or pain), and hyposensitivity, that is attributable to diminished nerve function (such as anaesthesia or hypaesthesia). The incidence of hyposensitivity is significantly lower than the incidence of hypersensitivity. Time is an important factor in assessment of sensory disturbance. Patients may develop sensory disturbance immediately post-operation or later on[9,23]. This was evidenced by Abdullah *et al.*[18] who implemented a three-year follow-up study to compare ICBN preservation and division.

Assa *et al.*[26]. performed an eighteen-month follow-up trial focusing on 46 radical mastectomies. Thirty-three involved the ordinary ICBN dissection, and only 13 cases preserved the ICBN. Assa and colleagues reported that all patients who experienced ICBN dissection suffered from mild anaesthesia to severe paraesthesia and throbbing sensations in the dermatome supplied by the ICBN (i.e. the inner part of the arm). On the other hand, of the 13 patients whose ICBN was preserved, only one complained of a mild throbbing sensation. The procedure of ICBN preservation does not prolong the operation time significantly[26]. Assa and colleagues also argued that the procedure of peeling off the fatty and lymphatic tissues from the nerve does not increase the risk of metastatic spread as the same procedure is performed with the thoracodorsal and nerve to serratus anterior.

Torresan *et al.*[9]. evaluated the impact of ICBN preservation during ALND. They found that the preservation of the ICBN is a possible and well-tolerated technique with a very good impact on sensory disturbance in the arm. Additionally, it does not affect the operation time or the number of dissected lymph nodes. Chirappapha *et al.*[20]. also estimated the effect of ICBN preservation during ALND. They reported that preservation of ICBN had no assistance in terms of improving sensation.

Blondeel *et al.*[27]. detected that though some sensation was discovered to be restored to skin flaps that lacked innervation, flaps that had undergone neurotization were found to have higher-quality sensation, earlier spontaneous sensation recovery, and a greater possibility of restoring erogenous sensation[27]. Subsequently, many studies have shown similar results; even though some sensation may return spontaneously, using a sensate flap underlying an autologous flap yields better results[28,29].

Neuromodulation is another suggested way to restore sensation. Voltage and current-regulated electrical neural stimulation (ENS) are technologies that have previously been used widely in neuroprosthetics research and clinical application[30].

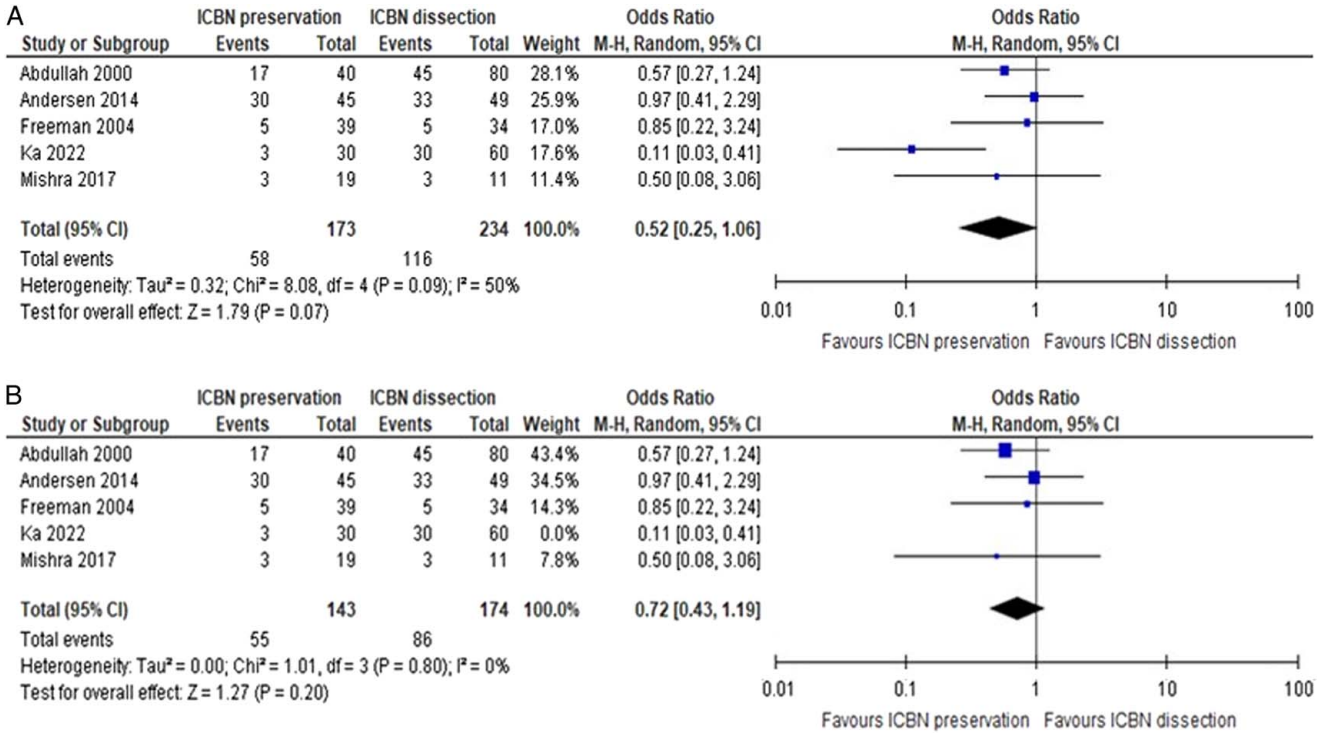

Figure 5. Forest plots of odds ratio. (A) Numbness; (B) numbness after sensitivity analysis. ICBN, intercostobrachial nerve.

Neuromodulation, which includes pharmaceutical, electrical, and optogenetic modulation, is primarily responsible for the modulation of neuronal activity[31]. Unfortunately, as of today, most studies on breast reconstruction outcomes and neurotization have methodological limitations. Notably, there is a lack of prospective studies and RCTs[32,33].

Future perspective

The debate between preservation versus dissection of the ICBN during breast cancer surgeries is likely to continue in the future. However, with advancements in surgical techniques and technology, it is possible that a more nuanced approach will emerge.

One possible future perspective is that surgeons will increasingly opt for nerve-sparing techniques that preserve the ICBN whenever possible. This may involve using more precise surgical instruments and imaging technologies to identify and avoid damaging the nerve during surgery. Additionally, surgeons may develop new approaches, such as: nerve monitoring systems and robotic-assisted surgery, to breast cancer surgery that minimize the need for ICBN dissection altogether. Another possibility is that researchers will continue to investigate the long-term effects of ICBN preservation versus dissection on patient outcomes. This could lead to a better understanding of which patients are most likely to benefit from nerve-sparing techniques, as well as which patients may be at higher risk for complications if the nerve is preserved.

Ultimately, the decision to preserve or dissect the ICBN should be made on a case-by-case basis, considering factors such as tumour size, lymph node involvement, and patient preferences. Surgeons should also consider alternative techniques such as

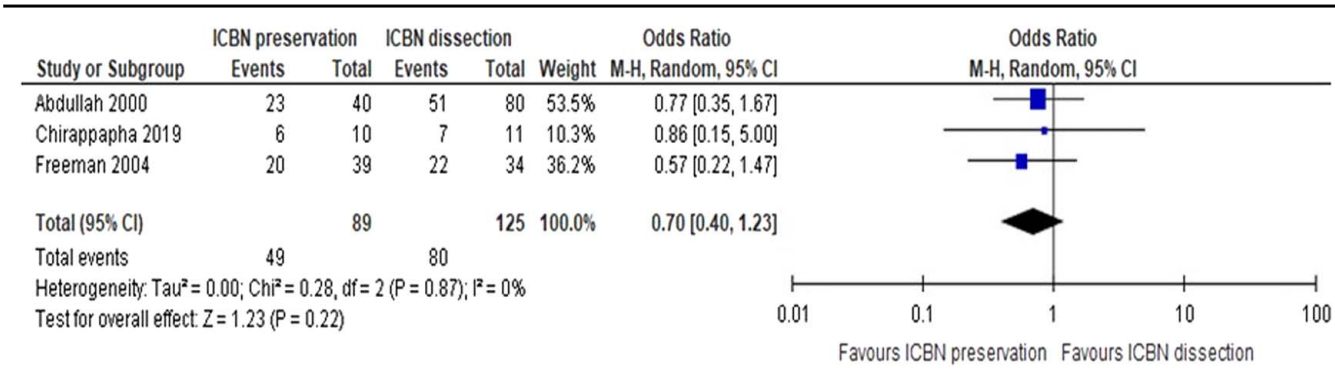

Figure 6. Forest plots of odds ratio in diminished sensation. ICBN, intercostobrachial nerve.

sentinel lymph node biopsy or targeted axillary dissection that may help reduce damage to surrounding nerves while still achieving effective cancer treatment.

Limitations

The major limitations in this study included: (1) a limited number of experimental studies, including a small sample size reporting assessment of analgesia and hyperaesthesia, making it difficult to generate strong evidence from their pooled analysis, and (2) we observed a marked heterogeneity in some outcomes, which can be accredited to the discrepancy in the period of intervention. Therefore, we recommend further well-designed and high-quality studies with an increased sample size to enhance the possibility of providing level 1 evidence using meta-analysis.

Conclusion

Our meta-analysis reveals that preservation of the ICBN through axillary lymph node dissection, when compared to its dissection, appeared to decrease the risk of some sensory disturbance parameters. Future analysis on a broader scale population is needed to more strongly assess the efficacy of ICBN preservation on a wider range of parameters.

Ethical approval

Not applicable.

Patient consent

Not applicable.

Source of funding

Not applicable.

Author contribution

N.M. A.-D.: conceptualization (lead); writing—original draft. A.M.K.: conceptualization (supporting); writing—original draft. K.A. A.: software. A.T.A., A.Y.B., T.L.: writing—original draft. K.A., A.K., J.A. F., S.J.L.: writing—review and editing.

Conflicts of interest disclosure

Not applicable.

Research registration unique identifying number (UIN)

The PROSPERO registration number for this study is CRD42022320452.

Guarantor

All authors.

Data availability statement

On reasonable request, the supporting data of this study's findings can be provided by the corresponding author.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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