Systematic Review

Eur J Breast Health 2025; 21(1): 1-8
DOI: 10.4274/ejbh.galenos.2024.2024-8-1

Adverse Effects of Intraparenchymal and Peritumoral Application of Isosulfan Blue Dye in Sentinel Lymph Node Mapping in Breast Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

We investigate the evidence for adverse effects of intraparenchymal and peritumoral application of isosulfan blue dye in sentinel lymph node (SLN) mapping in breast cancer patients. A meta-analysis on the adverse effects of intraparenchymal and peritumoral application of isosulfan application in SLN mapping was conducted using Medline and Embase databases up to 2023. Procedure-based adverse reactions were divided into three grades: Grade I (allergic skin reactions), Grade II (hypotension) and Grade III (requiring vasopressor support). Heterogeneity was expressed with I-squared and tau statistics. Subgroup analysis was conducted for administrative route. Univariable meta-regression was performed to assess dose-response effect on adverse reactions. Sensitivity analysis was conducted using fixed effect modelling. A total of 19,183 patients were identified from eight studies. The pooled total adverse event rate after isosulfan administration was 11.65 events per 1,000 patients [95% confidence interval (CI) 7.44–18.19]. The rate of Grade I reactions was 7.96 per 1,000 (95% CI 4.08-15.46); Grade II 0.08 per 1,000 (95% CI 0.00–1.31), Grade III 1.86 per 1,000 (95% CI 0.94–3.66), with no reported mortalities. Intraparenchymal administration was associated with 15.16 events per 1,000 (95% 8.64–26.45), versus 7.04 events per 1,000 (95% CI 5.24–9.45) in peritumoral administration (p=0.02). Univariable meta-regression did not show a significant association between volume of dye infused and total adverse events (-0.164 events per mL, 95% CI -0.864 to 0.534, p=0.645). Isosulfan has low adverse event rates regardless of injection technique or volume administered. Clinicians should have a high level of confidence in its use as an agent for SLN mapping, especially when administering it peritumorally.

Keywords: Breast neoplasms; isosulfan; sentinel lymph node mapping; systematic review; adverse events

Cite this article as: Agilinko J, Borakati A, Yoong A, Pratheepan P, Samlalsingh S. Adverse effects of intraparenchymal and peritumoral application of isosulfan blue dye in sentinel lymph node mapping in breast cancer: a systematic review and meta-analysis. Eur J Breast Health. 2025; 21(1): 1-8

Key Points

- Isosulfan blue has an acceptable safety profile for sentinel lymph node mapping in breast cancer surgery.
- Intraparenchymal, intraparenchymal administration of isosulfan blue has a significantly higher adverse event rate than peritumoral administration.
- There was no dose-response relationship between isosulfan administration and the incidence of adverse events.

Introduction

Breast cancer is the second most common cause of female cancer mortality in the UK, after lung cancer (1). The sentinel lymph node (SLN) is the first node receiving lymphatic drainage from the breast tumour bed, and SLN status is an important determining factor in breast cancer prognosis, patient survival and treatment outcomes (2, 3). The introduction of SLN biopsy is one of the greatest advances in the surgical treatment of breast cancer. Following the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (the ALMAC) trial by Mansel et al. (4), SLN mapping is widely accepted as the gold standard technique in axillary lymph node mapping, and has an equivalent oncological outcome, with reported lower complication rates, compared to axillary node dissection (AND). AND involves the dissection of the entire axillary lymph node chain and results in greater morbidity relating to lymphoedema and injury to key stractures such as the axilliary vein, and in a considerable percentage of cases, the

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Received: 23.10.2024
Accepted: 29.10.2024
Available Online Date: 01.01.2025

histopathological results following AND are negative, which means it could have been avoided. With the increasing use of SLN mapping, and its diagnostic accuracy therefore, AND is reserved for patients with axillary lymph node disease after SLN mapping.

Current SLN mapping agents include a variety of blue dyes and radioisotopes (5, 6). The principal problems involved with the latter, are their technological complexity and high costs. Different blue dyes have been used in SLN mapping and include methylene blue, patent blue and isosulfan blue, with similar reported rates of diagnostic accuracies in the setting of SLN mapping in breast cancer (7, 8).

Methylene blue is readily available and considered less expensive than the other two dyes. Although, it has a lower allergic and dermatological and allergic side-effect profile side effect profile compared to patent blue and isosulfan dyes, it is associated with skin necrosis and multi-systemic effects, especially the cardiovascular system and GI tract at higher concentrations (9). Isosulfan blue, an aniline dye (2.5-disulfan isomer of patent blue), was first introduced as an agent in SLN mapping by Giuliano et al. (10). It operates by binding to albumin in the lymphatic system in the axilla, allowing the sentinel node to be delineated. Its adverse effect profile, including allergic skin reactions, soft tissue necrosis and oxygen desaturation causing significant morbidity to patients, have been described in previous studies (11-14).

The aim of this meta-analysis was to synthesize evidence about the adverse effects of isosulfan blue dye in SLN mapping to raise awareness amongst clinicians. To the best of our knowledge, this is the first Level 1 study evaluating the adverse effects of intraparenchymal and peritumoral application of isosulfan dye in SLN mapping in breast cancer.

Materials and Methods

Search Strategy

The meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (15). Medline and Embase databases were searched from 1999 to 2023, inclusive. Search terms included "adverse", "reaction", "isosulfan", "blue", "dye", "sentinel", "lymph", "node", "biopsy", "breast", "cancer" together with the Boolean Operators "AND" and "OR".

Inclusion criteria were: 1) Breast cancer; 2) SLN mapping or biopsy; and 3) Use of isosulfan blue dye. Exclusion criteria were: 1) Sentinel node mapping in other cancers, such as cutaneous melanoma; 2) Single patient case reports; and 3) Non-English language papers. These criteria were applied throughout the titles, abstract screening stages and the full-text article reviewing process.

Data Extraction

Quantitative data were extracted for demographics, volume of isosulfan blue dye and grade of adverse reaction.

We used the 3-level classification of adverse reaction previously described by Montgomery et al. (16): Grade I included skin changes such as urticaria, pruritis, and rash; Grade II reaction included hypotension (systolic blood pressure <70 mmHg) following administration; and Grade III reaction was defined as hypotension, and other cardiovascular and respiratory complications requiring vasopressor support.

Statistical Analysis

Meta-analysis of proportions was conducted on included papers as described by Barker et al. (17) to generate a pooled event rate for all events and grouped by grade. A generalised linear mixed model was used with random effects and a logit transformation to generate the pooled event rate. A Clopper-Pearson interval was used to calculate 95% confidence intervals (CIs). A p-value <0.05 was regarded as statistically significant. Funnel plots and Egger's test were used to assess publication bias.

Meta-analyses are presented as forest plots with events per 1000 patients as the outcome measure. Heterogeneity is expressed using the I-squared and tau statistics. Subgroup analysis by route of administration of isosulfan was conducted for all events. The chi-squared test was used to assess statistically significant differences between groups. Univariable meta-regression was performed on studies reporting volume of administration to assess for a dose-response effect of isosulfan administration on adverse reactions. A sensitivity analysis was also conducted using fixed effect modelling and is presented as a Supplementary Figure 1. All analyses were conducted with R version 4.3.0 (R Foundation, Vienna, Austria) with meta version 6.5 (18) and metafor version 4.2 (19) packages.

Results

Search Results

The initial electronic database search yielded 105 articles, with three additional studies being included following screening of references. From these, 10 articles were duplicates and 75 were non-full text articles (Figure 1).

Twenty-three full-text articles were subsequently reviewed and a further 15 articles were excluded for various reasons (non-breast cancers such as cutaneous melanomas, other blue dyes used in combination with isosulfan blue dye and results not fully available). A further 10

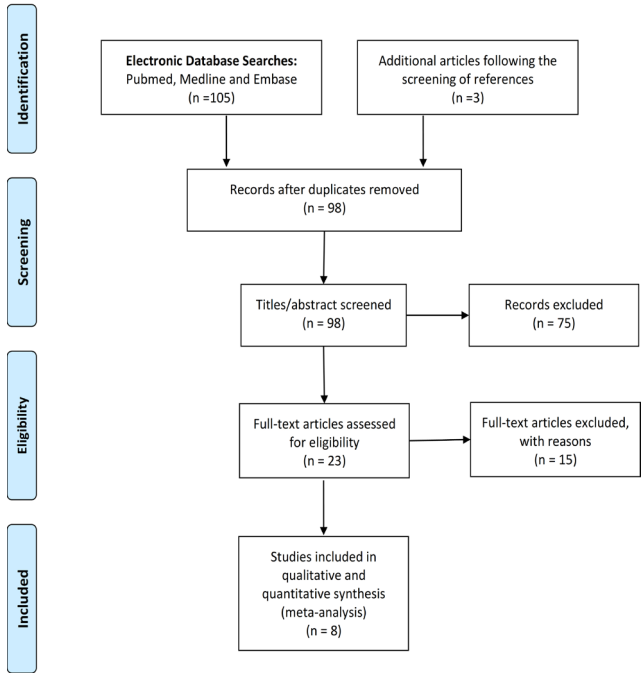

Figure 1. PRISMA flowchart of inclusion and exclusion of studies

articles were excluded as they were case reports. A further five articles were excluded because they only investigated the changes in pulse oximetry following isosulfan blue administration with no clear cut-off desaturation level established for definition of hypoxaemia.

Finally, eight articles were included for qualitative and quantitative analysis.

Summary of Results

The selected studies included 19,183 patients. The route of administration was reported in 14,205 cases (intraparenchymal injection=7,955 patients; peritumoral injection = 6,250 patients.) The mean volume of isosulfan blue dye injected from 12,110 cases was 4.3 mL (SD ± 0.98).

There were 231 adverse events reported across all studies after isosulfan administration: Grade I reactions were seen in 184 patients (79.7%); Grade II in 4 patients (1.7%) and Grade III reactions in 43 patients (18.6%) (Table 1). Thirty-eight patients required vasopressin support and 19 patients required admission to the intensive care unit for post-procedure monitoring. However, none of the patients required emergency intubation. There was no mortality associated with isosulfan blue dve use.

Meta-Analysis

The pooled total adverse event rate after isosulfan administration was 11.65 events per 1,000 patients (95% CI 7.44-18.19, Figure 2). The rate of grade I reactions was 7.96 per 1,000 (95% CI 4.08–15.46, Figure 3); grade II 0.08 per 1,000 (95% CI 0.00–1.31, Figure 4) and grade III 1.86 per 1,000 (95% CI 0.94–3.66, Figure 5).

On subgroup analysis by route of administration, intraparenchymal administration of isosulfan was associated with a total adverse event rate of 15.16 events per 1,000 (95% 8.64–26.45), whilst peritumoral administration had an adverse event rate of 7.04 events per 1,000 (95% CI 5.24–9.45). This difference in adverse event rates was significant at $p = 0.02$ (Figure 6).

Univariable meta-regression of studies reporting the volume of isosulfan did not show a significant association of volume infused with total adverse events (-0.164 events per mL, 95% CI–0.864 to 0.534, $p = 0.645$). Funnel plotting of the included studies was symmetrical (Figure 7) and Egger's test gave $p = 0.239$, implying publication bias.

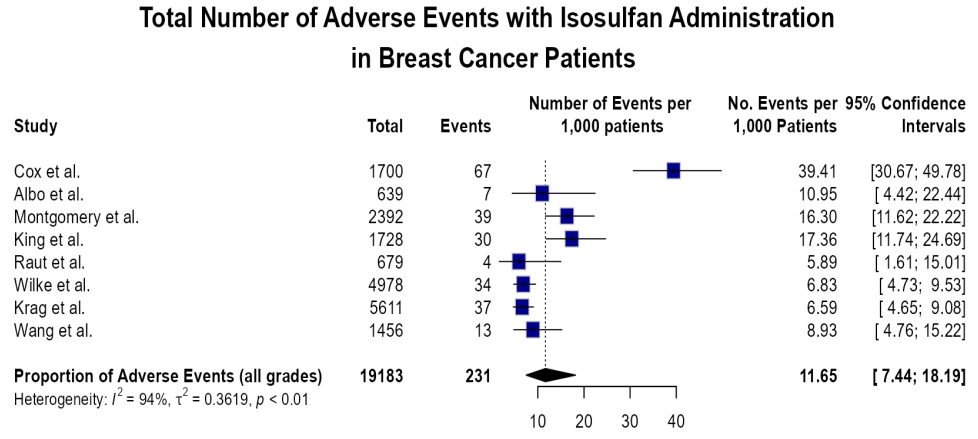

Figure 2. Forest plot of random effects meta-analysis of all adverse events after isosulfan administration

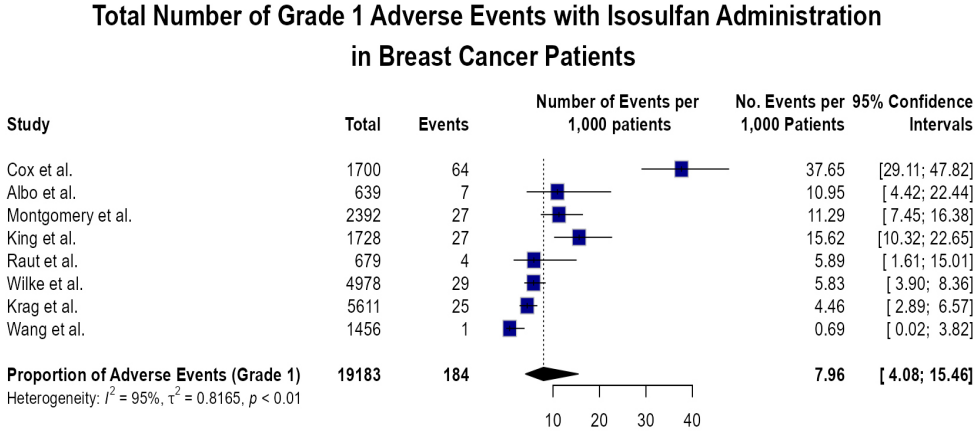

Figure 3. Forest plot of random effects meta-analysis of grade i reactions after isosulfan administration

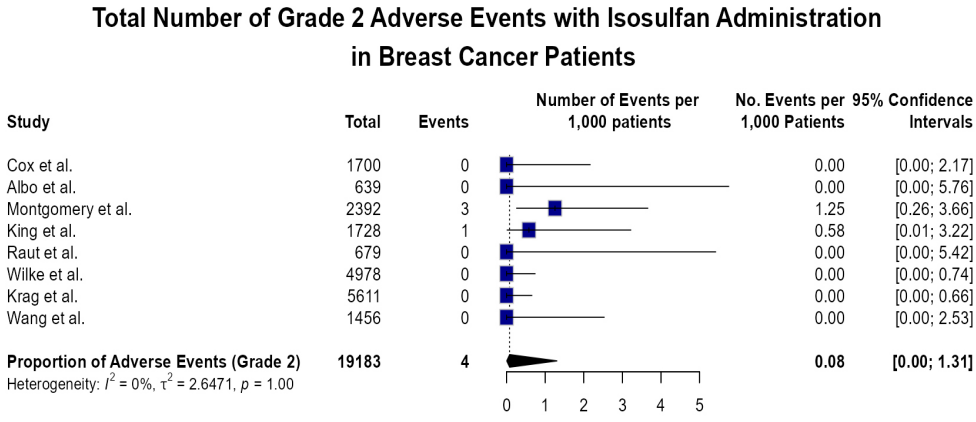

Figure 4. Forest plot of random effects meta-analysis of grade ii reactions following isosulfan administration

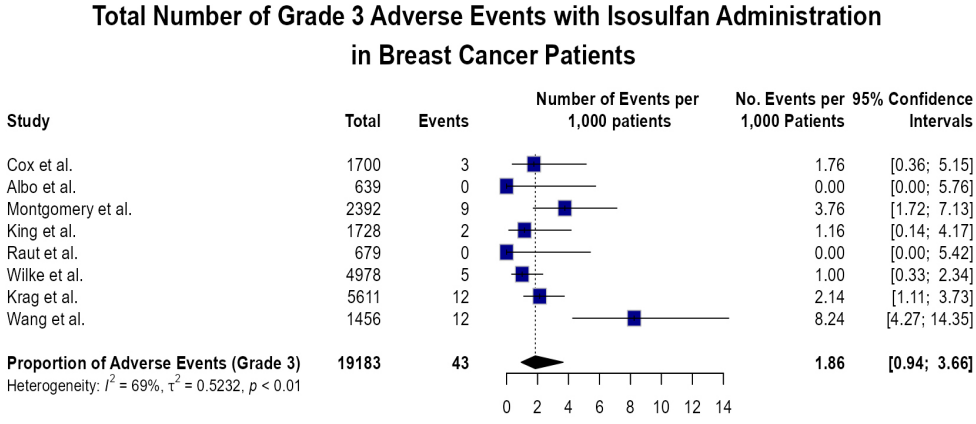

Figure 5. Forest plot of random effects meta-analysis of grade iii reactions after isosulfan administration

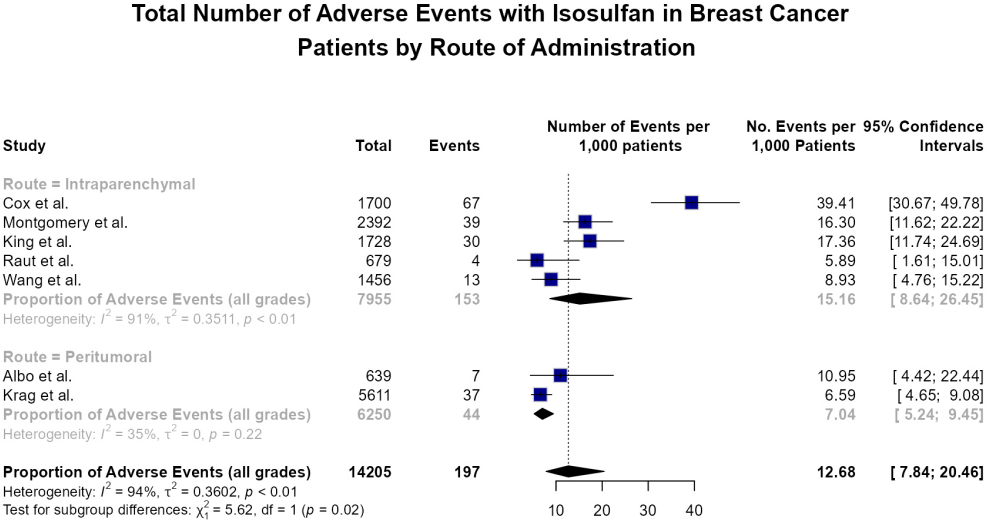

Figure 6. Subgroup analysis of all adverse events after isosulfan administration by route of administration

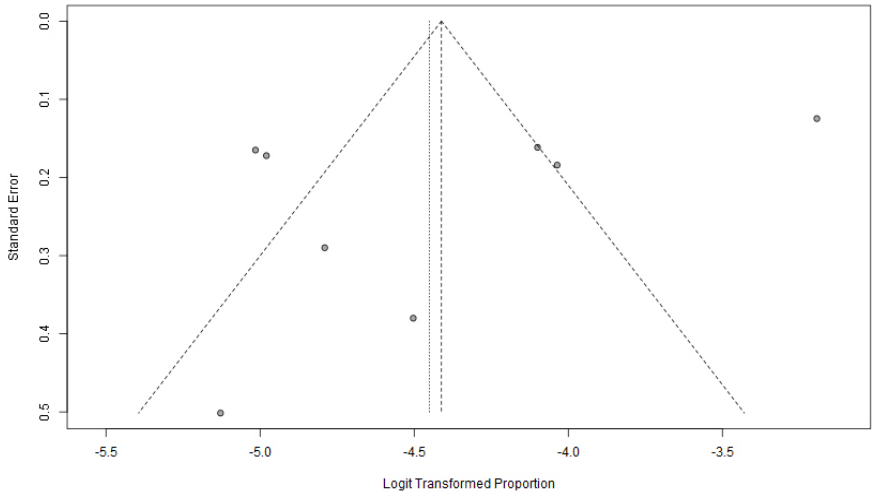

Figure 7. Funnel plot of included studies by total adverse even

Discussion and Conclusion

This is the first meta-analysis investigating the safety profile of intraparenchymal and peritumoral application of isosulfan blue as a sentinel node mapping agent in breast cancer. We show low adverse event rates, of which the majority are minor and non-life threatening, associated with its use. We further show that peritumoral infiltration of the dye is associated with significantly lower rates of adverse events than intraparenchymal infiltration. Our findings have broad implications for the use of isosulfan more widely in breast cancer surgery and in the technique for administration.

The paradigm of early breast cancer management has shifted from AND towards conservative diagnostic techniques, such SLN mapping in axillary staging, with comparative diagnostic outcomes with both techniques, while the latter is associated with a lower rate of lymphoedema as well as nerve and vascular injuries (3, 20).

Techniques for mapping and identification of the SLN can be broadly divided into radioisotopes and dyes (5, 6). Some investigators prefer the use of nuclear medicine techniques to identify the SLN due to the greater simplicity of those techniques compared to the use of dyes. Compared to dyes, however, they are associated with higher operative costs and some studies have highlighted their technological complexity (21). In this regard, the use of dyes is more economically viable, and this is important in healthcare resource allocation especially in developing countries. With these disadvantages of nuclear medicine, blue dyes have become popular SLN mapping agents. The commonly used blue dyes are methylene blue, isosulfan blue and patent blue. Identification rates of SLN are similar to that obtained with nuclear medicine techniques, reported to be as high as 98% in recent reports (23). Furthermore, once the SLN is identified, accuracy is the same, irrespective of the method used and the lymph node detection rate.

Isosulfan blue dye (2.5-disulfan isomer of patent blue) was one of the first dyes used in SLN mapping. It was adopted to breast cancer patients from Morton et al. (24) work in cutaneous melanoma (10). It is however not without adverse reactions which can compromise patient safety. Some of the frequently reported adverse reactions include changes to pulse oximetry reading, and soft tissue and body fluid discolouration, as well as allergic and anaphylactic (type 1 hypersensitivity) reactions (25-27).

Methylene blue, on the other hand, is a derivative of phenothiazine, and offers three main advantages over patent blue and isosulfan dyes: it is more readily available, cost less and appears to be a lower risk of anaphylaxis compared to the other dyes (9, 28). It does however have some disadvantages in comparison to isosulfan blue dyes. Firstly, it diffuses more rapidly in peripheral tissues, staining a larger portion of the breast with the blue dye and, to a certain extent, hampering the procedure. There are also reported cases of skin necrosis, cardiovascular and gastro-intestinal symptoms associated with high doses of methylene blue use (29, 30).

In our meta-analysis, we employed the 3-level systematic classification (Grades I-III) used by Montgomery et al. (16). Comparatively, we found our pooled total rate of adverse reaction to be 1.2%, similar to 1.6% in the review by Montgomery et al. (16) at the Memorial Sloan-Kettering Cancer Centre. Our study revealed that Grade I reactions were the most common following administration of isosulfan blue dye.

Proposed mechanisms for adverse reactions to isosulfan blue dye can be categorised into antibody-mediated, or anaphylactic, and antibody-independent, or anaphylactoid, pathways (31). Antibody-mediated, immediate-type hypersensitivity reactions have been suspected as the cause of reactions to patent blue dye, mediated by immunoglobulin E antibodies. Anaphylactic reactions usually occur after previous sensitisation to isosulfan blue and related patent blue agents, and are associated with Grade II and III reactions, but can result in Grade I reactions too.

Another study by Kalimo et al. (32) reported skin reactions on skin prick test two weeks following blue dye injection. They recommended a role for pre-lymphography skin prick testing to reduce Grade I reactions.

It is interesting that although isosulfan blue contains sulfa (SO_2NH_2) moieties, patients with a sulfa allergy are not more likely to experience

an allergic reaction to isosulfan blue dye, as reported in the study by Montgomery et al. (16), where only 2.6% of patients with a sulfa allergy manifested an allergic reaction to isosulfan blue.

Grade II and III reactions (anaphylactic shock with or without vasopressor support) was first reported in 1985 by Longnecker and colleagues following the administration of 0.5ml of 1% isosulfan blue subcutaneously (33).

Albo et al. (13) also report a Grade III reaction rate of 1.1% in their study of 1456 patients where 12 patients experienced severe cardiovascular compromise within 15 to 30 minutes following administration of isosulfan blue. In their study, all affected patients required aggressive resuscitation and subsequently admission to intensive care for post-operative monitoring. Our study reports a rate of 0.08 per 1,000 of Grade II reactions and 1.86 per 1000 patients of Grade III reactions. Our rates of Grade III events are lower than those reported by Albo et al. (13) and another study by Cox et al. (34). Despite our low rates of Grade II and III reactions in the meta-analysis, close monitoring is important in Grade II and II reactions as biphasic anaphylactic reaction with patent blue dye and its monomers, such as isosulfan, have been reported by Liang and Carson (25) when hypotensive episodes occurred 15 minutes and two hours following blue dye exposure.

In the study conducted by Raut et al. (27) the authors evaluated the role of glucocorticoids in reducing the adverse effects of isosulfan blue dye. In their study, patients who were given isosulfan blue dye were also administered a glucocorticoid, diphenhydramine, and famotidine intravenously just before or at induction of anaesthesia. Preoperative prophylaxis was found to reduce the severity, but not the overall incidence, of adverse reactions of isosulfan blue dye. Crucially, there were no life-threatening reactions noted in patients treated with preoperative prophylaxis. Based on these results, there is potentially a role for routine administration of prophylaxis to patients receiving isosulfan blue for lymphatic mapping and SLN mapping.

Subgroup analysis by route of administration of isosulfan was conducted for all events. We showed a much lower rate of adverse reactions associated with peritumoral administration of the dye compared to intraparenchymal administration. It is widely agreed that the accuracy of SLN detection is irrespective of route of dye administration but our study suggest the lower rate of adverse reactions with peritumoral injection makes it superior. It is also worth stating that another technique which has increasingly come into practice is subareolar injection. This approach is however associated with nipple complications which may be a problem for immediate breast reconstruction. Our study did not focus on this technique.

Studies reporting volume of administration to assess for dose-response effect of isosulfan administration showed no effect on the rate of adverse reactions, further reinforcing the safety of the dye.

Current consensus guidelines in the UK (35), US (36) and Europe (37) recommend blue dye and radioisotope localisation of SLN, but do not specify the actual dye used as diagnostic accuracies in SLN mapping associated with all commonly used dyes are comparable. Indocynanine green (ICG) is a newer agent which fluoresces proportionally to its uptake by tissues. This fluorescence can be quantified with cameras used intra-operatively after injection with the brightest points corresponding to lymph nodes. ICG has been shown to have superior detection rates of positive SLNs compared to blue dye and radioisotope mapping (38). Adverse event rates are lower than isosulfan, while cost per application is similar (39). This method continues to be evaluated and has not found widespread adoption. The use of newer techniques may require a learning curve as well as investment in new equipment, such as detectors, which may be prohibitive.

Isosulfan blue continues to be used widely despite the known limitations, as an accurate mapping modality, with a wide evidence base and familiarity amongst surgeons. This study strengthens the case for isosulfan as a SLN mapping agent by quantifying its low overall adverse event profile and extremely low rate of serious adverse events.

Footnotes

Authorship Contributions: Surgical and Medical Practices: J.A., P.P., S.S.; Concept: J.A., A.Y.; Design: J.A., A.B., A.Y.; Data Collection or Processing: J.A., A.B., A.Y.; Analysis or Interpretation J.A., A.B., A.Y.; Literature Search: J.A., A.B., A.Y.; Writing: J.A., A.B., A.Y.

Conflict of Interest: No conflict of interest declared by the author.

Financial Disclosure: The author declare that this study received no financial. disclosure.

Table 1. Summary of included studies

Author, year	Evidence level	No. of patients	Route used	Volume used (mL)	Total Reactions	Grade 1 reaction	Grade 2 reaction	Grade 3 reaction
Cox et al. (33)	IV	1700	Intraparenchymal	5	67	64	0	3
Albo et al. (13)	III	639	Peritumoral	-	7	7	0	0
Montgomery et al. (16)	III	2392	Intraparenchymal	3.9	39	27	3	9
King et al. (39)	III	1728	Intraparenchymal	2.8	30	27	1	2
Raut et al. (26)	III	679	Intraparenchymal	5	4	4	0	0
Wilke et al. (40)	III	4978	-	-	34	29	0	5
Krag et al. (41)	II	5611	Peritumoral	5	37	25	0	12
Wang et al. (25)	III	1456	Intraparenchymal	-	13	1	0	12

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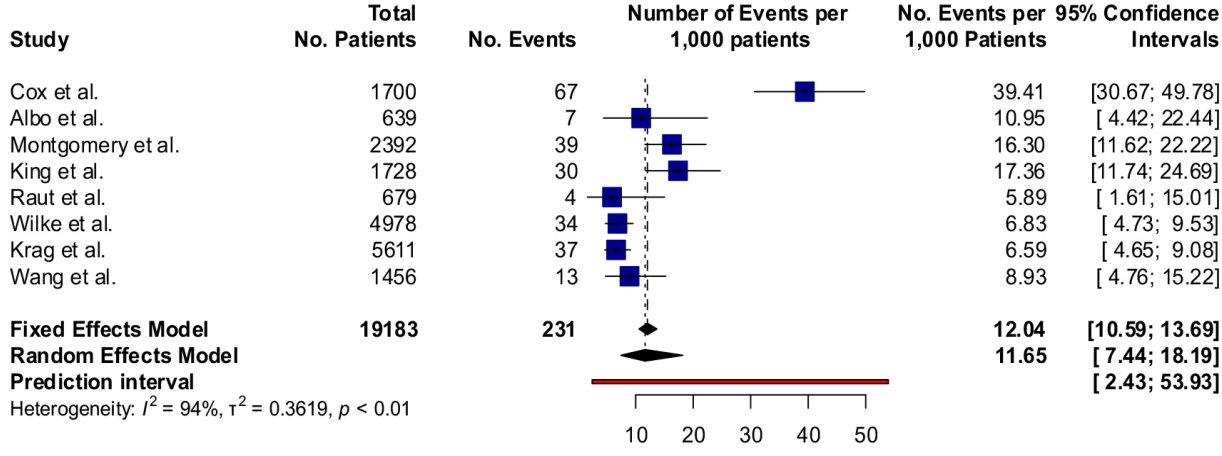

Supplementary Figure 1. Sensitivity analysis of meta-Analysis of total adverse events after isosulfan administration with fixed effects model