Systematic review

Systematic review of intravenous methylene blue in parathyroid surgery

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Background: **Methylene blue is an intraoperative adjunct for localization of enlarged parathyroid glands. The availability of preoperative and other intraoperative localization methods, and the reported adverse effects of methylene blue make its routine use debatable. The aim of this study was to perform a systematic review of the use of methylene blue in parathyroidectomy.**

Methods: **A systematic review of English-language literature in MEDLINE and Scopus databases on the use of intravenous methylene blue in parathyroid surgery was carried out.**

Results: **There were no randomized clinical trials. Thirty-nine observational studies were identified, of which 33 did not have a control arm. The overall median staining rate for abnormal parathyroid glands was 100 per cent. The median cure rates in the methylene blue and no-methylene blue arms were 100 and 98 per cent respectively. Neurotoxicity was reported in 25 patients, all of whom were taking serotonergic medication.**

Conclusion: **Observational evidence suggests that methylene blue is efficacious in identifying enlarged parathyroid glands. Toxicity appears to be mild in the absence of concomitant use of serotonin reuptake inhibitors. The effectiveness of methylene blue in the context of currently used preoperative and intraoperative localization techniques has yet to be shown.**

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Introduction

Several factors make intraoperative identification of the parathyroid glands difficult, including size, coexistent thyroid pathology, and supernumerary and ectopic glands. Experienced endocrine surgeons occasionally find parathyroidectomy challenging to perform. Methylene blue is available for use as an intraoperative adjunct to aid localization of enlarged parathyroid glands during surgery for hyperparathyroidism. This technique was pioneered by Dudley in 1971[1] and has since been implemented by many other surgeons[2–6].

The benefits of using methylene blue in parathyroid surgery have not been defined. Although several centres and surgeons routinely use the dye as an intraoperative aid, current literature discourages this practice[7], or advises on reducing the dose administered[8]. This is partly in response to both serious[9,10] and minor[1] adverse effects reported in the literature. Serious adverse effects postulated to be due to serotonin toxicity have been attributed to an interaction between methylene blue and serotonergic medication[8].

Currently there are no published systematic reviews that examine the use of methylene blue. In the light of apparent variation in practice, debate over its use and the lack of an in-depth understanding of the effectiveness and adverse effects of methylene blue use in parathyroid surgery, a systematic review was undertaken.

Methods

A literature search of the MEDLINE (via PubMed) and Scopus databases was performed on 27 October 2010 using the terms ‘methylene blue’ AND ‘parathyroid’. The titles

and/or abstracts of all retrieved articles were screened by two researchers to include all original articles that described the use of intravenous methylene blue during parathyroid surgery in humans. Single case reports were included to allow for the reporting of adverse effects related to administration of methylene blue. Articles that did not have an English translation, reviews and letters were excluded.

Data from each article, including details of the study population, dose and methods of administration of methylene blue, findings at surgery, cure rates and untoward/adverse effects of methylene blue, were extracted by one researcher using a standardized pro forma. For each study, staining rates and cure rates were calculated separately for single-gland disease (SGD) and multigland disease (MGD), wherever possible.

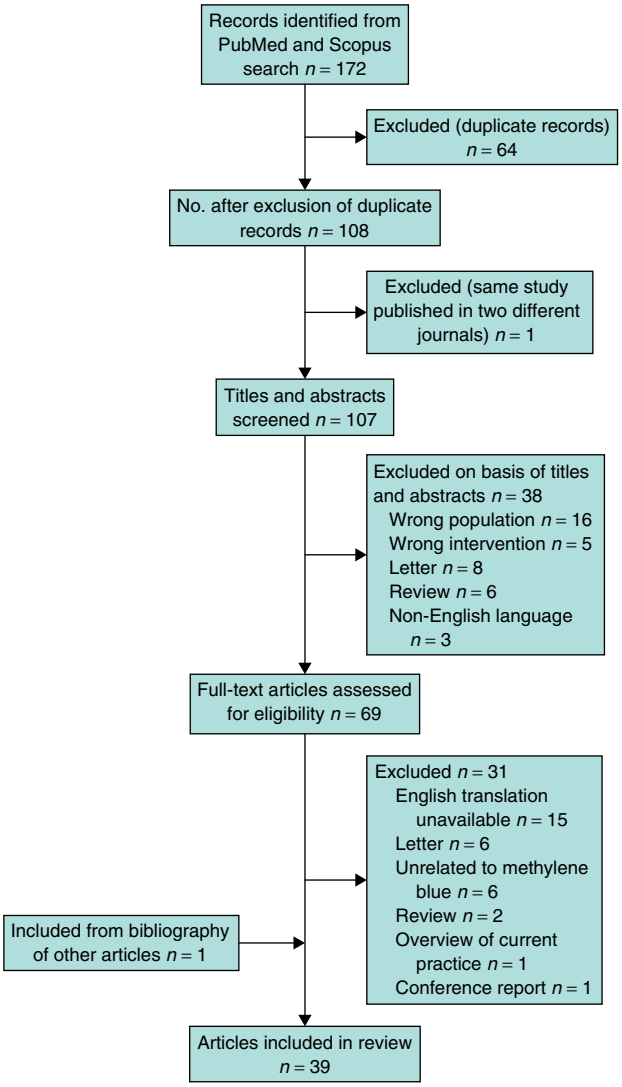

Fig. 1 PRISMA flow diagram for studies included in the systematic review

Statistical analysis

Individual staining and cure rates were described as numbers, and overall rates as median (range).

Results

Fig. 1 shows the process of inclusion and exclusion of articles identified by the search. Thirty-nine studies[1–6,11–43] were eligible for inclusion in the review. Twenty-nine[1–6,13–15,19,23,24,26–30,32–43] examined the role of methylene blue as an intraoperative adjunct and ten studies[11,12,16–18,20–22,25,31] reported primarily on serious adverse events. There were no randomized clinical trials (RCTs) that evaluated the efficacy or effectiveness of methylene blue in parathyroid surgery. A meta-analysis of the data set was not performed as the included studies were heterogeneous with respect to the populations studied, the specific nature of the interventions used and reported outcomes.

Study characteristics

Table S1 (supporting information) outlines the characteristics of all studies included in the analysis. A total of 1899 patients were included in the methylene blue arm and 435 in the no-methylene blue arm. Only seven studies[6,19,24,28,33,36,38] were clearly labelled as being prospective in nature. Six studies[14,23,29,35,36,42] were conducted with a control (no methylene blue) arm, of which three included historical controls[14,35,42]. Twelve of the included studies were single case reports.

Methylene blue infusion techniques

Of the 39 studies, 20[1,2,4,5,16,18,19,21,25,27,30,32–36,39,40,42,43] administered methylene blue at a dose ranging from 5 to 6 mg/kg, with a further 11 studies[6,11,12,14,20,22,23,26,28,29,38] using 7·5 mg/kg as part of their clinical practice (*Table S2*, supporting information). The dosage was varied in two institutions[3,17], and six studies[13,15,24,31,37,41] did not report on the exact dose used. Twenty-four studies[1–5,14,16,17,19,20,23,24,27–29,32,33,35–37,39,40,42,43] administered methylene blue via a 200–500-ml fluid infusion volume, three studies[6,12,30] used an infusion volume of 100 ml, and 12[11,13,15,18,21,22,25,26,31,34,38,41] did not report on the volume of fluid infused.

Twenty-eight studies[1–6,11,13,14,16–19,20,23,24,27–30,33,35,36,38–41,43] initiated the methylene blue infusion before

skin incision, whereas one study reported initiation at skin incision[42]. Seven studies[12,15,22,26,31,32,37] did not report on the timing of infusion. One case report[21] described the methylene blue administration as an intravenous bolus immediately after intubation, and two other reports[25,34] described starting the infusion during surgery.

Staining of abnormal parathyroid glands with methylene blue

Single case reports were excluded from the calculation of staining rates. In addition, 14[4,5,14,17,19,27–29,34,37–39,42,43] studies were excluded as they did not clearly document the proportions of stained abnormal parathyroid glands. One of these studies was related primarily to documentation and description of untoward/adverse events related to the administration of methylene blue[17].

The median staining rate in 243 patients from 11 studies with SGD was 100 (range 83–100) per cent[1–3,6,13,23,24,30,32,33,40], and that in 144 patients from 13 studies with MGD was 100 (67–100) per cent[1–3,6,13,23,24,30,32,33,35,36,40] (*Table 1*). The overall median staining rate (SGD and MGD) was 100 per cent.

Cure rates in methylene blue and no-methylene blue groups

Single case reports were excluded from the calculation of cure rates. Only patients who had undergone first-time surgery were considered for the analysis. In the four studies[14,27,42,43] that reported cure rates in the methylene blue arm (without specifying rates for SGD and MGD), the median cure rate in 911 patients was 98 (89–100) per cent. Two[14,42] of these four studies reported a median cure rate of 99 (98–100) per cent for 269 patients in the no-dye arm.

In the methylene blue group, 12 studies[2–6,13,23,28,30,33,37,38] and 13 studies[2–6,13,23,28,30,33,35,37,38] reported on cure rates following first-time surgery for SGD and MGD respectively. All 287 patients with SGD were cured and the median cure rate in 141 patients with MGD was 100 (66–100) per cent.

One of the six studies with a no-methylene blue arm reported cure rates in patients with MGD; surgery corrected hyperparathyroidism in nine of the 12 patients[35]. Three studies[23,29,36] did not report any information on cure rates, whereas two other studies[14,42] reported overall cure rates without differentiating SGD from MGD.

The overall median cure rate (combining SGD and MGD) was 100 per cent for the methylene blue arm (17 studies) and 98 per cent for the no-methylene blue arm (3 studies).

Untoward and adverse events related to methylene blue infusion

Of the 39 studies, 25 described untoward effects related to methylene blue. Commonly reported effects include pseudocyanosis, temporary urine discoloration (blue) and pseudohypoxia[1,4,23,24,30,40,43]. These effects were not quantified.

Table 1 Seventeen studies, including case reports, reporting on methylene blue staining of abnormal parathyroid glands

	Single-gland disease		Multigland disease		
Reference	No. of patients or glands	No. of diseased glands stained	No. of patients	No. of abnormal glands observed	No. of diseased glands stained
Pollack *et al.*[12], 2009	1	1	0	–	–
Baloch *et al.*[13], 2007	12	12	4	16	16
Moriyama *et al.*[15], 2007	1	1	0	–	–
Alexander *et al.*[21], 2006	0	–	1	1	1
Kuriloff and Sanborn[23], 2004	30	29	5	12	12
Soomro and Moizuddin[24], 2004	4	4	1	3	2
Chandran *et al.*[26], 2003	1	1	0	–	–
Orloff[6], 2001	18	15	5	16	11
Takei *et al.*[30], 1999	12	12	3	5	5
Horii *et al.*[32], 1998	1	1	1	1	1
Müslümanoğlu *et al.*[33], 1995	10	10	12	26	26
Derom *et al.*[3], 1993	65	64/65*	49	200	195/196*
Kobayashi *et al.*[35], 1988	0	–	13	50	47
Bland *et al.*[36], 1985	0	–	23	91	82
Wheeler and Wade[40], 1982	72	70	18	55	46
Bambach and Reeve[2], 1978†	10	10	9	29	29
Dudley[1], 1971	9	9	1	4	4

*Unclear whether one adenoma that failed to stain was in a patient with a single or double adenoma; †one patient was excluded from this analysis as information regarding the underlying pathology was not available.

Table 2 Reported adverse effects of methylene blue

Adverse event	Study type	No. of patients	Comments
Neurotoxic sequelae (including, clonus, hyper-reflexia, confusion, agitation, disorientation, difficulty in arousing, tachycardia, hypertension)	Retrospective[14,17] Single case reports[11,12,16,18,20,22,25,31]	17 of 325 (5·2)*	Amalgamation of information from both retrospective studies[14,17] showed that all 17 patients who suffered from this adverse event were taking a serotonin reuptake inhibitor. All patients recovered, except one, who had a cardiopulmonary arrest and died[14]
Transient pain at infusion site	Prospective[6,28,36] Retrospective[35,39]	33 of 99 (33)	One study[6] addressed this issue by reducing the rate of MB infusion
Nausea	Prospective[38] Retrospective[35,39]	4 of 83 (5)	One study reported a case attributable to rapid MB infusion[38]. Another study discontinued the infusion in one patient, which resolved the nausea[39]
Local oedema/thrombophlebitis	Prospective[28]	3 of 39 (8)	
'Local effects'	Prospective[28]	27 of 39 (69)	
Transient angina	Prospective[36]	1 of 23 (4)	Attributed to rapid MB infusion
Patient unable to tolerate infusion	Retrospective[3]	1 of 120 (0·8)	
Mild armpit pain	Prospective[33]	†	

Values in parentheses are percentages. *Single case reports not included in this calculation. †Exact number of patients who had the adverse event was not reported. MB, methylene blue.

Table 3 False-positive staining with methylene blue during parathyroidectomy

Reference	No. of patients	No. of patients with lymph node staining	No. of normal parathyroid glands stained	No. of patients with thyroid gland staining
Kuriloff and Sanborn[23], 2004	35	Reported but not quantified	41 of 89 (46)	Reported but not quantified
Orloff[6], 2001	23	0	4 of 4 (100)	Reported but not quantified
Takei *et al.*[30], 1999	15	Reported but not quantified	No normal glands seen	Reported but not quantified
Derom *et al.*[3], 1993[3]	120	4 of 120	Staining seen in 50 patients	11 of 120 (nodules or cysts)
Kobayashi *et al.*[35], 1988	13	1 of 13	No normal glands seen	Reported but not quantified
Devine *et al.*[39], 1983	30	Reported but not quantified	NA	Reported but not quantified
Wheeler and Wade[40], 1982	90	0	82 of 116 (70·7)	Reported but not quantified
Cox *et al.*[42], 1979	9	0	No normal glands seen	3 of 10*
Bambach and Reeve[2], 1978	20	0	5 of 13 (38)	3† of 20
Gordon *et al.*[5], 1975	17	2 lymph nodes	4 of 18 (22)	7 of 17
Dudley[1], 1971‡	10	0	14 of 14 (100)	Reported but not quantified

Values in parentheses are percentages of the total number of normal parathyroid glands seen. *One of the nine patients had a reoperation; †two fat lobules and one thymic cyst; ‡strap muscle staining was noted in this study. NA, data not available.

Eighteen studies[3,6,11,12,14,16–18,20,22,25,28,31,33,35,36,38,39] made note of serious adverse events (*Table 2*); eight[11,12,16,18,20,22,25,31] of these were single case reports. The adverse events included transient postoperative neurotoxicity, pain at the infusion site and nausea. One death was documented in a patient given methylene blue who suffered from neurotoxicity; the authors reported that 'cardiomyopathy may have contributed to her decline'[14].

False-positive staining with methylene blue

False-positive staining was reported to occur in normal parathyroid glands, lymph nodes, thyroid tissue, thymic cyst and adipose tissue.

Eleven studies commented on false-positive staining with the use of methylene blue (*Table 3*). Normal parathyroid glands were reported to be stained in seven studies; the staining rate varied from 22 to 100 (median 59) per cent calculated from six studies[1,2,5,6,23,40]. One study was not able to quantify the number of glands stained, but did report that stained glands were observed in 50 separate patients[3].

Lymph nodes were reported to be stained in six studies[3,5,23,30,35,39], but details were inadequate in three studies[23,30,39] that used the terms 'occasional' and 'some' rather than reporting actual numbers. A total of five stained lymph nodes were reported in two studies[3,35], whereas the

staining of 'two lymph nodes' was reported in the third study[5] (*Table 3*).

Staining of the thyroid was also stated in 11 studies[1–3,5,6,23,30,35,39,40,42]; seven studies[1,6,23,30,35,39,40] did not provide quantitative information (*Table 3*). The remaining four studies[2,3,5,42] reported 24 instances (14·4 per cent) of thyroid staining in 167 patients.

One other study also reported false-positive staining[4]. Three of 60 biopsies taken during the study interval were found not to be parathyroid tissue on histological examination, despite blue staining. The origins of the stained tissue were not reported.

Operating times

Of the six studies that contained a methylene blue and no-methylene blue group, four[14,29,36,42] stated that operating times were reduced when the dye was used. This time reduction was significant in two of the studies: Han and colleagues[14] showed a reduction in operating time of 7 and 12 min in the minimally invasive and neck exploration arms respectively ($P = 0{\cdot}026$), whereas Bland and co-workers[36] reported a mean reduction of approximately 27 min in patients undergoing bilateral neck exploration ($P < 0{\cdot}01$).

Discussion

The absence of high-level evidence to evaluate the usefulness of methylene blue in parathyroid surgery is an example of how surgical practice is influenced more by tradition and experience, and less by evidence. This review has, however, shown methylene blue to be efficacious, with staining rates of enlarged parathyroid glands approaching 100 per cent[3,13,23]. Findings from the review also illustrated high cure rates associated with methylene blue use. However, these results cannot be compared with those in patients in whom methylene blue was not used owing to the paucity of reported data and the absence of standardized reporting.

Untoward effects such as discoloration of urine and skin are common features in patients given methylene blue[1,4,23,24,30,40,43], but these appeared to be harmless and self-limiting. However, serious adverse effects include neurotoxicity[11,12,14,16–18,20,22,25,31] associated with disorientation, agitation, tachycardia and hypertension, amongst other clinical signs in the postoperative patient. Of two case series that reported on patients taking serotonin reuptake inhibitors (SRIs)[14,17], 17 of 45 patients on SRIs experienced neurotoxic adverse events. None of the 280 patients who were not on SRIs developed neurotoxicity. All patients except one made a full recovery. Eight case reports also documented neurological adverse effects in patients concurrently taking serotonergic medication. A further four patients with adverse neurotoxic events were reported in letters to the editor, and these were excluded from the systematic review[9,10,44]. It is likely that these neurological effects were due to serotonin toxicity. The mechanism of serotonin toxicity is attributed to the inhibition of monoamine oxidase (MAO) by methylene blue[45]. MAO is an enzyme involved in the degradation of the neurotransmitter, serotonin. Serotonin toxicity may therefore occur following the co-administration of a SRI and a MAO inhibitor[46]. It is recommended, therefore, that the use of methylene blue be avoided in patients taking a SRI[8,11,14,47]. This recommendation is supported by the UK Medicine and Healthcare products Regulatory Agency, which has also been notified directly of a further three patients demonstrating postoperative neurotoxicity[48].

The main limitations of the review include the paucity of comparative data between patients who did and did not receive methylene blue, the absence of standardized reporting, and the likelihood of publication bias. Cure rates were variably defined, if at all, in the studies included in the review.

The ability of methylene blue to stain enlarged parathyroid glands makes it a potentially useful intraoperative identification tool. Despite recent attention drawn to the development of serotonin toxicity, this problem seems to be uncommon if the dye is avoided in patients taking serotonergic medication. Doubts remain over whether the use of methylene blue is effective in improving cure rates in the context of currently used localization tools, and this cannot be addressed with currently available observational evidence.

Disclosure

The authors declare no conflict of interest.

References

1 Dudley NE. Methylene blue for rapid identification of the parathyroids. *Br Med J* 1971; **3**: 680–681.
2 Bambach CP, Reeve TS. Parathyroid identification by methylene blue infusion. *Aust N Z J Surg* 1978; **48**: 314–317.
3 Derom AF, Wallaert PC, Janzing HM, Derom FE. Intraoperative identification of parathyroid glands with methylene blue infusion. *Am J Surg* 1993; **165**: 380–382.
4 Gavilán J, Gavilán C, Tomás MD. Methylene blue infusion for intraoperative identification of the parathyroid glands. *Laryngoscope* 1986; **96**: 1389–1390.
5 Gordon DL, Airan MC, Thomas W, Seidman LH. Parathyroid identification by methylene blue infusion. *Br J Surg* 1975; **62**: 747–749.

6 Orloff LA. Methylene blue and sestamibi: complementary tools for localizing parathyroids. *Laryngoscope* 2001; **111**: 1901–1904.
7 Harrison BJ, Triponez F. Intraoperative adjuncts in surgery for primary hyperparathyroidism. *Langenbecks Arch Surg* 2009; **394**: 799–809.
8 Gillman PK. Methylene blue implicated in potentially fatal serotonin toxicity. *Anaesthesia* 2006; **61**: 1013–1014.
9 Patel AS, Singh-Ranger D, Lowery KA, Crinnion JN. Adverse neurologic effect of methylene blue used during parathyroidectomy. *Head Neck* 2006; **28**: 567–568.
10 Khavandi A, Whitaker J, Gonna H. Serotonin toxicity precipitated by concomitant use of citalopram and methylene blue. *Med J Aust* 2008; **189**: 534–535.
11 Rowley M, Riutort K, Shapiro D, Casler J, Festic E, Freeman WD. Methylene blue-associated serotonin syndrome: a 'green' encephalopathy after parathyroidectomy. *Neurocrit Care* 2009; **11**: 88–93.
12 Pollack G, Pollack A, Delfiner J, Fernandez J. Parathyroid surgery and methylene blue: a review with guidelines for safe intraoperative use. *Laryngoscope* 2009; **119**: 1941–1946.
13 Baloch MN, Aslam T, Maher M. Surgical management of hyperparathyroidism. *J Coll Physicians Surg Pak* 2007; **17**: 683–685.
14 Han N, Bumpous JM, Goldstein RE, Fleming MM, Flynn MB. Intra-operative parathyroid identification using methylene blue in parathyroid surgery. *Am Surg* 2007; **73**: 820–823.
15 Moriyama T, Kageyama K, Nigawara T, Koyanagi M, Fukuda I, Yashiro H *et al*. Diagnosis of a case of ectopic parathyroid adenoma on the early image of ^{99m}Tc-MIBI scintigram. *Endocr J* 2007; **54**: 437–440.
16 Khan MA, North AP, Chadwick DR. Prolonged postoperative altered mental status after methylene blue infusion during parathyroidectomy: a case report and review of the literature. *Ann R Coll Surg Engl* 2007; **89**: W9–W11.
17 Sweet G, Standiford SB. Methylene-blue-associated encephalopathy. *J Am Coll Surg* 2007; **204**: 454–458.
18 Ng BK, Cameron AJ, Liang R, Rahman H. [Serotonin syndrome following methylene blue infusion during parathyroidectomy: a case report and literature review.] *Can J Anesth* 2008; **55**: 36–41.
19 Mihai R, Gleeson F, Buley ID, Roskell DE, Sadler GP. Negative imaging studies for primary hyperparathyroidism are unavoidable: correlation of sestamibi and high-resolution ultrasound scanning with histological analysis in 150 patients. *World J Surg* 2006; **30**: 697–704.
20 Mathew S, Linhartova L, Raghuraman G. Hyperpyrexia and prolonged postoperative disorientation following methylene blue infusion during parathyroidectomy. *Anaesthesia* 2006; **61**: 580–583.
21 Alexander TH, Beros AD, Orloff LA. Twice-recurrent primary hyperparathyroidism due to parathyroid hyperplasia in an ectopic supernumerary gland. *Endocr Pract* 2006; **12**: 165–169.
22 Majithia A, Stearns MP. Methylene blue toxicity following infusion to localize parathyroid adenoma. *J Laryngol Otol* 2006; **120**: 138–140.
23 Kuriloff DB, Sanborn KV. Rapid intraoperative localization of parathyroid glands utilizing methylene blue infusion. *Otolaryngol Head Neck Surg* 2004; **131**: 616–622.
24 Soomro MS, Moizuddin. Role of methylene blue infusion in per-operative localization of parathyroid glands. *J Pak Med Assoc* 2004; **54**: 199–202.
25 Bach KK, Lindsay FW, Berg LS, Howard RS. Prolonged postoperative disorientation after methylene blue infusion during parathyroidectomy. *Anesth Analg* 2004; **99**: 1573–1574.
26 Chandran M, Deftos LJ, Stuenkel CA, Haghighi P, Orloff LA. Thymic parathyroid carcinoma and postoperative hungry bone syndrome. *Endocr Pract* 2003; **9**: 152–156.
27 Schell SR, Dudley NE. Clinical outcomes and fiscal consequences of bilateral neck exploration for primary idiopathic hyperparathyroidism without preoperative radionuclide imaging or minimally invasive techniques. *Surgery* 2003; **133**: 32–39.
28 Flynn MB, Bumpous JM, Schill K, McMasters KM. Minimally invasive radioguided parathyroidectomy. *J Am Coll Surg* 2000; **191**: 24–31.
29 Martin RC II, Greenwell D, Flynn MB. Initial neck exploration for untreated hyperparathyroidism. *Am Surg* 2000; **66**: 269–272.
30 Takei H, Iino Y, Endo K, Horiguchi J, Maemura M, Koibuchi Y *et al*. The efficacy of technetium-99m-MIBI scan and intraoperative methylene blue staining for the localization of abnormal parathyroid glands. *Surg Today* 1999; **29**: 307–312.
31 Stanford BJ, Stanford SC. Postoperative delirium indicating an adverse drug interaction involving the selective serotonin reuptake inhibitor, paroxetine? *J Psychopharmacol* 1999; **13**: 313–317.
32 Horii Y, Iino Y, Maemura M, Takei H, Horiguchi J, Koibuchi Y *et al*. Usefulness of technetium-99m-methoxyisobutylisonitrile imaging and intraoperative staining technique using methylene blue for localization: two cases of hyperfunctioning parathyroid lesions. *Kitakanto Medical Journal* 1998; **48**: 367–371.
33 Müslümanoğlu M, Terzioğlu T, Ozarmağan S, Tezelman S, Güloğlu R. Comparison of preoperative imaging techniques (thallium technetium scan and ultrasonography) and intraoperative staining (with methylene blue) in localizing the parathyroid glands. *Radiol Med* 1995; **90**: 444–447.
34 O'Leary DP, White HJ. Parathyroidectomy for hyperparathyroidism associated with renal disease. *Ann R Coll Surg Engl* 1995; **77**: 97–101.
35 Kobayashi S, Miyakawa M, Sugenoya A, Senga O, Kaneko G, Yokozawa T *et al*. An evaluation of the intraoperative staining technique using methylene blue for the detection of hyperplastic parathyroid glands. *Jpn J Surg* 1988; **18**: 729–731.

36 Bland KI, Tidwell S, von Fraunhofer JA, Morris RR, McCoy MT, Wathen RL. Intraoperative localization of parathyroid glands using methylthionine chloride/tetramethylthionine chloride in secondary hyperparathyroidism. *Surg Gynecol Obstet* 1985; **160**: 42–48.
37 Botha JR, Diamond TH, Meyers AM, Myburgh JA. Parathyroid disease. Part I. The management of primary hyperparathyroidism. *S Afr J Surg* 1985; **23**: 43–46.
38 Sherlock DJ, Holl-Allen RT. Intravital methylene blue staining of parathyroid glands and tumours. *Ann R Coll Surg Engl* 1984; **66**: 396–398.
39 Devine RM, van Heerden JA, Grant CS, Muir JJ. The role of methylene blue infusion in the management of persistent or recurrent hyperparathyroidism. *Surgery* 1983; **94**: 916–918.
40 Wheeler MH, Wade JS. Intraoperative identification of parathyroid glands: appraisal of methylene blue staining. *Am J Surg* 1982; **143**: 713–716.
41 Lavelle MA. Parathyroid adenoma stained with methylene blue. *J R Soc Med* 1980; **73**: 462–463.
42 Cox RJ, Moore DB, Wolfman EF Jr. Localization of the parathyroid glands by intraoperative methylene blue staining. *Surg Gynecol Obstet* 1979; **148**: 769–770.
43 Drews M, Paszkowski J, Stawny B, Banasiewicz T, Hermann J, Meczyński M *et al*. Comparison of parathyroid gland localization techniques in patients treated due to gland hyperfunction. *Polski Przeglad Chirurgiczny* 2003; **75**: 821–828.
44 Martindale SJ, Stedeford JC. Neurological sequelae following methylene blue injection for parathyroidectomy. *Anaesthesia* 2003; **58**: 1041–1042.
45 Ramsay RR, Dunford C, Gillman PK. Methylene blue and serotonin toxicity: inhibition of monoamine oxidase A (MAO A) confirms a theoretical prediction. *Br J Pharmacol* 2007; **152**: 946–951.
46 Bodner RA, Lynch T, Lewis L, Khan D. Serotonin syndrome. *Neurology* 1995; **45**: 219–223.
47 Ng BKW, Cameron AJ. The role of methylene blue in serotonin syndrome: a systematic review. *Psychosomatics* 2010; **51**: 194–200.
48 Medicines and Healthcare products Regulatory Agency. Methythioninium chloride (methylene blue): CNS toxicity with serotonergic drugs. *Drug Safety Update* 2008; **1**: 5.

Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Characteristics of 39 studies evaluating the use of methylene blue in parathyroid surgery (Word document)

Table S2 Details of methylene blue infusion technique as described in the 39 included studies (Word document)

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Commentary

Systematic review of intravenous methylene blue in parathyroid surgery (*Br J Surg* 2012; 99: 1345–1352)

Infusion of methylene blue dye before parathyroidectomy was introduced in the early 1970s as an intraoperative adjunct to identify abnormal parathyroid glands. Methylene blue has been considered by some surgeons to be safe and cost-effective during parathyroidectomy, by itself or as a complement to other preoperative or intraoperative localization tools[1]. Despite the high expectations and despite being inexpensive and readily available, methylene blue has had only limited acceptance by the endocrine surgical community, in contrast to ultrasonography, sestamibi scintigraphy and rapid intraoperative parathyroid hormone assay. Of note, recent literature has discouraged the routine use of methylene blue[2], owing mainly to the lack of evidence of significant benefits for the patient in terms of decreased duration of surgery and increased cure rate, and to the risk of serious neurological adverse effects. The latter is particularly true for patients treated with selective serotonin-uptake inhibitor therapy, because of the monoamine oxidase-inhibiting properties of methylene blue[2]. In this context, the paper by Patel and colleagues has the merit of being the first systematic review of the English literature on this topic. Unfortunately, owing to the lack of pertinent studies with a high level of evidence, the authors failed to demonstrate unequivocally any significant advantage when methylene blue is used for intraoperative parathyroid localization. Indeed, only large prospective comparative studies could clarify the role of methylene blue in parathyroid surgery.

On the other hand, it should be remembered that the success rate of parathyroidectomy, with both conventional and minimally invasive approaches, without the utilization of methylene blue, exceeds 95 per cent in the hands of experienced surgeons, with minimal morbidity. Methylene blue infusion, which is potentially dangerous[3], cannot replace detailed and thorough knowledge of embryology and anatomy as well as adequate surgical experience, which are the key factors for successful parathyroidectomy.

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Disclosure

The author declares no conflict of interest.

References

1 Orloff LA. Methylene blue and sestamibi: complementary tools for localizing parathyroids. *Laryngoscope* 2001; **111**: 1901–1904.
2 Han N, Bumpous JM, Goldstein RE, Fleming MM, Flynn MB. Intra-operative parathyroid identification using methylene blue in parathyroid surgery. *Am Surg* 2007; **73**: 820–823.
3 Vutskits L, Briner A, Klauser P, Gascon E, Dayer AG, Kiss JZ *et al*. Adverse effects of methylene blue on the central nervous system. *Anesthesiology* 2008; **108**: 684–692.