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ARTICLE

Does methylene blue increases capsular contracture in immediate breast reconstruction with silicone implant? An experimental study

Abbas Albayati[a], Burak Ozkan[a], Alev O. Atilgan[b], Tugce Sencelikel[c], Cagri A. Uysal[a] and Nilgun M. Ertas[a]

[a]Department of Plastic Reconstructive and Aesthetic Surgery, Faculty of Medicine, Baskent University, Ankara, Turkey; [b]Department of Clinical Pathology, Faculty of Medicine, Baskent University, Ankara, Turkey; [c]Department of Biostatistics, Faculty of Medicine, Baskent University, Ankara, Turkey

ABSTRACT

Recently, most of the immediate breast reconstructions following mastectomy are being carried out with the use of silicone implants. In these patients, methylene blue is being used for the detection of sentinel lymph nodes. This experimental study was performed to determine the effect of methylene blue on capsular contracture around breast implants. Thirty-two Sprague Dawley rats were divided into 4 groups. Custom made silicone blocks were placed on the back of animals. In group 1, the incision was closed without performing any additional procedure. In group 2 (control), 0.1 mL of 0.9% normal saline was instilled into the pocket. Group 3 and 4 (study groups) received 0.1 and 0.2 mL of 1% methylene blue, respectively. On postoperative day 60, implants and capsular tissue were extracted. Capsule formation was evaluated both macroscopically and microscopically. The histological evaluation included capsule thickness, inflammation, neovascularization, and fibrosis gradients. Regarding capsule thickness, there were statistically significant differences between groups 1–3, 1–4, 2–3, and 2–4. Although there were more moderate and severe inflammation gradients in groups III and IV, there was no significant difference regarding inflammation severity between control and study groups. In respect of vascular proliferation, there was a statistically significant difference between control and study groups. Similarly, fibrosis gradients were higher in both groups 3 and 4. The study showed that the injection of methylene blue around silicone implants enhanced the formation of capsular contracture. In this case, the degree of contracture was independent of the dose given.

Abbreviations: CC: capsular contracture; MM: methylene blue; SLNB: sentinel lymph node biopsy; NS: normal saline; H&E: hematoxylin and eosin; D: dorsal; V: ventral; L: lateral; n: frequency.

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KEYWORDS
Blue dye; fibrosis; inflammation; Sentinel lymph node biopsy

Introduction

Whenever an implant is inserted in the body, the body reacts by forming a protective layer around the implant. Capsule formation is a physiological reaction around implants inserted in the body and is formed by inflammatory cells and fibroblasts. When this reaction is exaggerated, the condition is called capsular contracture (CC) which is a mechanophysical phenomenon characterized by shortening of the capsular tissue leading to distortion and a reduction in compliance of the breast implant. Although the exact etiology is unknown, studies have linked CC to an inflammatory response mediated by different cells like polymorphonuclear leukocytes, macrophages, fibroblast and mast cells [1]. CC is the most common and most disturbing complication after breast augmentation and breast reconstruction [2].

Methylene blue (MB) is a phenothiazine related heterocyclic aromatic molecule. Clinically, it is used in the treatment of methemoglobinemia and cases of resistant vasoplegic shock. Diagnostically, it is used in detection of sentinel lymph nodes in patients undergoing mastectomy. This method was first described by Guiliano et al. [3]. When MB is injected into the tissues, especially subdermally, the dye remains in dermal and subcutaneous tissues that are left after mastectomy. Once the implant is inserted in the setting of immediate breast reconstruction, its discoloration with the residual dye is inevitable. Blue discoloration of the implant is persistent for months or years. Advantages of MB are being inexpensive with an equivalent success rate in comparison to isosulfan blue. Nevertheless, various skin reactions may be seen at injection site due to aldehyde formation and a reduction in oxidation products. Thus leading to a cellular response characterized by macrophage activation and severe inflammation [4]. Stradling et al. [5] have reported an incidence around 21% of different skin reactions ranging from erythema to skin necrosis. Similarly, Lee JH et al. [6] reported a series of 6 cases of skin necrosis due to the use of MB in Sentinel Lymph Node Biopsy (SLNB) in patients undergoing mastectomy and immediate breast reconstruction. A previous study by Singh-Ranger G. et al. [7] have presented a case report of severe capsular contracture 9 months following breast reconstruction and was linked to MB injection. Independently of these studies, negative effects of MB on CC were observed clinically in our practice. Based on these findings, it was thought that MB may increase the incidence and the severity of CC around silicone implants stained with the dye in patients undergoing alloplastic breast reconstruction.

In this experimental study we aimed to investigate the effect of MB, which was instilled during the placement of silicone implant under the dorsum of the rat, and whether the outcome changes according to the dose of the dye used.

CONTACT Abbas Albayati albyati17@gmail.com Department of Plastic and Reconstructive Surgery, Faculty of Medicine, Baskent University, Azerbaycan cad 78/6 Bahcelievler, Ankara, Turkey

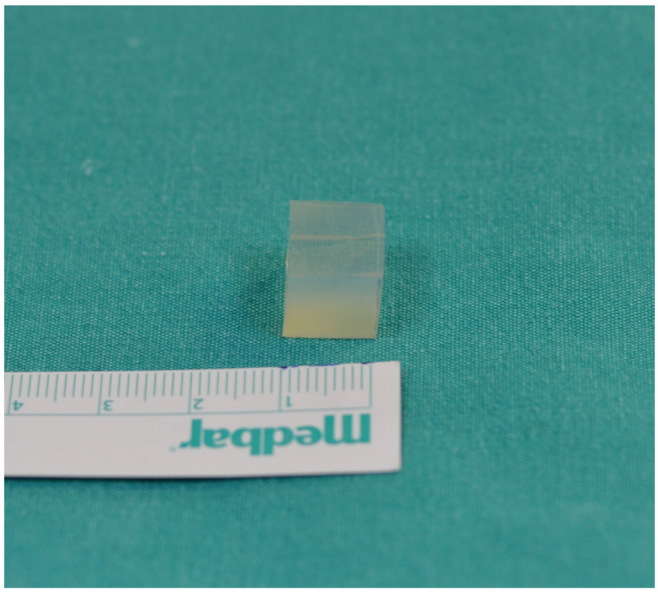

Figure 1. Custom-made silicone block.

Materials and methods

Animals and overview of the study

This study was performed with the approval of regional ethical committee for experimental research on animals (Project no: DA19/10 – 29 April 2019). Adult female Sprague-Dawley rats (300–350 g) were used. They were housed for at least 7 days before the experiment with under 23 °C with 12 h of light and dark cycles. Rats consumed standard raw chow and water *ad libitum*. A total of 32 rats were randomly divided into 4 groups as; sham group ($n = 8$), control group (sodium chloride 0.9%), study group 1 (low dose 1% MB) and study group 2 (high dose 1% MB).

Preparation of silicone implants

A cubic costum made silicone blocks of size $10 \times 10 \times 10$ mm were prepared by cutting a 9×7 cm solid silicone block (Mentor®, Santa Barbara, CA, USA) equally (Figure 1). The sharp edges of each implant were rounded up equally. Silicone blocks were sterilised by Ethilen Oxide.

Experimental model

Anesthesia was carried out by injection of 40 mg/kg ketamine (Ketalar®, Pfizer İnc., Istanbul, Turkey), 10 mg/kg xylazine (Rompun®, Bayer Inc. Istanbul, Turkey) intraperitoneally. Preoperatively, all animals received 50 mg of 5% enrofloxacin containing antibacterial solution (Baytril-k®, Bayer Inc. Istanbul, Turkey) intraperitoneally. Local antisepsis during surgical interventions was done by used of 10% povidone-iodine. An area of 8×8 cm over the dorsum of each rat was shaved and cleaned using 10% povidone-iodine. Talc-free gloves were used. A submuscular pocket of 1×1 cm dimensions was planned at right scapular region. A 2 cm incision was made perpendicular to the junction of midline and the level of iliac crest (Figure 2). A surgical plane deep to panniculous carnosus muscle was reached through minimal blunt dissection. To avoid unnecessary dissection that may lead to implant migration, silicone blocks were advanced with a surgical clamp toward the planned pocked (Figure 3). Meticulous haemostasis was done. A custom-made silicone block sized $10 \times 10 \times 10$ mm was inserted in a submuscular pocket on the back of each rat. Group 1 was a sham control group and no intervention was done. 0.1 ml of 0.9% Normal Saline (NS) was instilled in the pockets of rats of group 2 using a 1-cc syringe with a 26-gauge needle. Animals in group 3 and 4 received 0.1 and 0.2 ml of 1% methylene blue (IDOL Inc., Istanbul, Turkey) respectively (Figure 4). Incisions were closed in two layers with 4-0 silk (Doğsan, Istanbul, Turkey) sutures. Postoperative analgesia was maintained by 0.02 mg/kg fentanil (Sufenta®, Janssen Pharma Inc., Belgium) intraperitoneally. All assessments were made 60 days after surgery. At the end of study all rats were sacrificed by intraperitoneal injection of 150 mg/kg ketamine.

Macroscopic evaluation

Postoperatively animals were monitored daily for wound healing, weight loss and signs of infection. The skin overlying silicone blocks were evaluated for thinning and adherence to the blocks. After 60 days, an incision around silicone block was done wide enough to include the block with the capsule and the overlying skin. Furthermore, macroscopic evaluation included adhesions between capsule and the surrounding tissues, in addition to macroscopic vascularity over the capsule.

Histological evaluation

Tissue specimens were fixed in 10% neutral buffered formalin for 24 h. Tissue materials embedded in paraffin and sectioned to 4–6 μm width. Microscopic stains included hematoxylin and eosin (H&E) for inflammation and vascularity, and masson trichrome for collagen fibres. The stained materials were evaluated under light microscope (Olympus BX51, Tokyo, Japan) by a board-certified pathologist who was blinded to the treatment.

Measurement of capsular thickness

To quantitate capsular thickness, image analysis software (Olympus, U-TV1XC, Tokyo, Japan) was used. Capsule thicknesses were measured at three different areas in each slide. Dorsal (D; between silicone block and the skin), ventral (V; between silicone block and the underlying muscle) and lateral (L; on each side of silicone block) were measured. Mean capsule thickness for each area was measured from five different readings for each animal.

Neovascularization assessment by vascular density

Vascular proliferation in capsular tissue was evaluated as the number of small vessels under 200x magnification and was scored between 0 and 4 as follows; 0; no proliferation, 1; less than 10 vessel in a section, 2; 10–20 vessel in a section, and 3; more than 20 vessel in a section.

Inflammatory cell density

Inflammation gradient is the number of inflammatory cells counted per field area reflecting the intensity of capsule inflammation. Inflammation severity was scored from 0 to 4 according to the percentage of area occupied by inflammatory cells in each section as follows: 0; no inflammation, 1; mild inflammation (less than 25%), 2; moderate inflammation (25–50%), and 3; severe inflammation (more than 50%), as described previously in the literature [8,9].

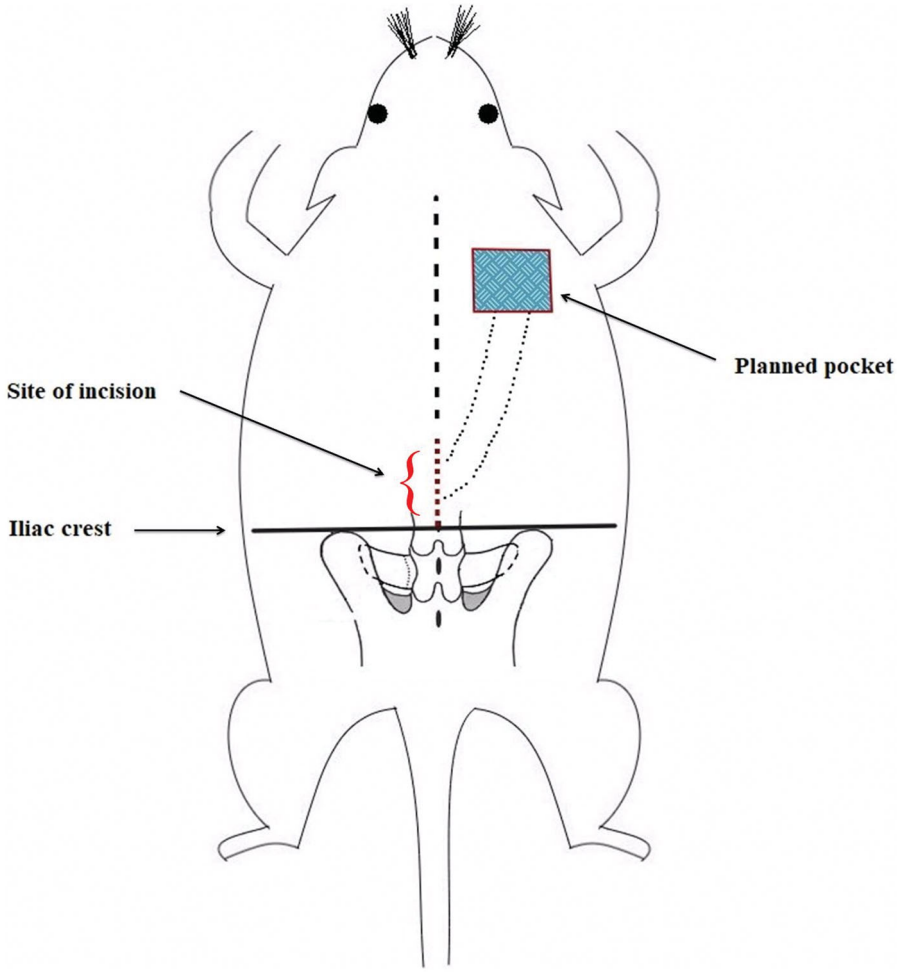

Figure 2. Illustration of surgical procedure.

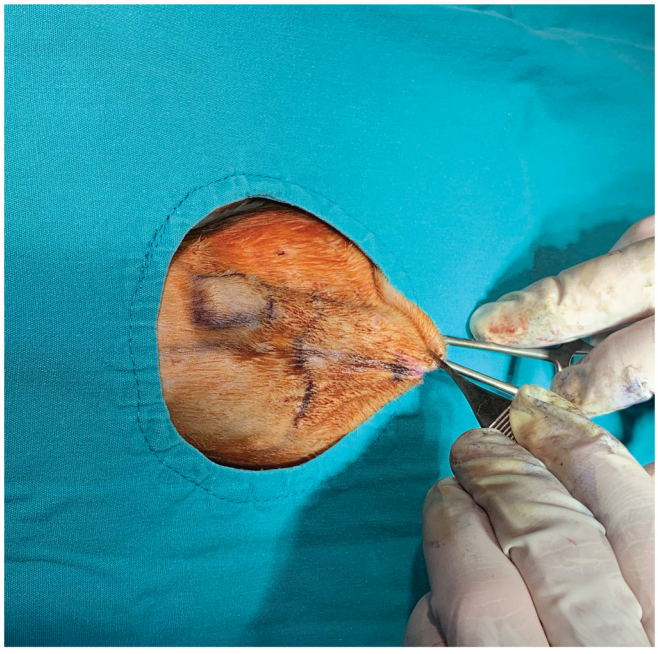

Figure 3. Placing of silicone block.

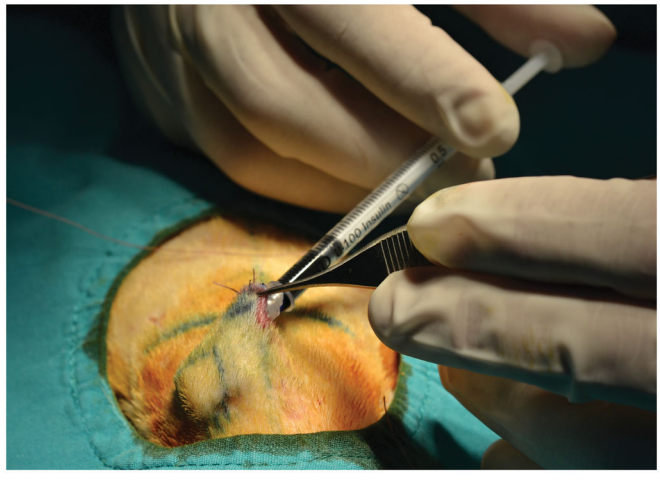

Figure 4. Instillation of methylene blue inside the surgical pocket.

Fibrosis gradient assessment

Section stained with Masson-Trichrome dye for the assessment of fibrosis according to the organization of collagen fibres. The percentage of capsular tissue affected by fibrosis was semi-quantitively analysed as follows: 0; no fibrosis, 1; mild fibrosis (less than 25%), 2; moderate fibrosis (between 25% and 50%), and 3; severe fibrosis (more than 50%), as described elsewhere in the literature [8,9].

Statistical analysis

The capsular thickness, vascular density, inflammation and fibrosis gradients were statistically evaluated between the groups. Since

the assumptions for parametric test are not met, median (minimum–maximum) was given for numerical measurements, and frequency (n) and percentage (%) for categorical data. Whether there was a significant difference among groups in term of numerical measurements was analysed by non-parametric Kruskal–Wallis test. The difference among groups was analysed using Multiple-comparison Dunn-Bonferroni test. Nonparametric Wilcoxon signed test was used to compare ventral and dorsal thicknesses taken from same rat. The analysis of categorical data was done using Fisher–Freeman–Halton Exact test. Values with a $p < 0.05$ were considered statistically significant. Analysis was performed using the Statistical Package for Social Sciences (SPSS for Windows, version 25.0, Chicago, IL, USA).

Results

During the course of the study, one animal of group II died on the second day of the experiment. There was a skin flap necrosis and implant exposure in one animal of group I and was excluded from the study.

Macroscopic assessment

No sign of infection was observed. Macroscopically silicone blocks were non-mobile and fixed to the dorsum of the rat at postoperative 60th day. In groups 3 and 4, the skin and surrounding tissues over silicone block were contracted given its cubic shape and blue discoloration was observed along the tunnel (Figure 5). During implant explantation, diffuse adhesion was noted between the capsule and the underlying muscles in groups 3 and 4, in comparison to groups 1 and 2 (Figure 6). Capsules from groups 3 and 4 had more vascular network compared to capsules of group 1 and 2 (Figure 7).

Figure 5. Lateral view of the skin contracted over the block. (A) Group 2, (B) group 3.

Microscopic assessment

Examination under light microscope showed a visible fibrous capsule around silicone capsules in subjects of all groups. Some specimens from group 3 and 4 showed silicone particles stained with MB (Figure 8).

Capsular thickness

The average capsular thickness was $53.66 \pm 1.96\,\mu m$ in group 1, $51.16 \pm 0.53\,\mu m$ in group 2, $100.46 \pm 10.88\,\mu m$ in group 3, and $93.35 \pm 4.42\,\mu m$ in group 4. There was no significant difference in terms of capsule thickness among dorsal, ventral and lateral areas within the same group ($p_{group\text{-}1} = 0.398$; $p_{group\text{-}2} = 0.866$; $p_{group\text{-}3} = 0.051$; $p_{group\text{-}4} = 0.263$; Table 1). Statistical analysis showed that capsule thicknesses were higher in groups 3 and 4 and there was a significant difference between group 1–3, group 1–4, group 2–3 and group 2–4 ($p = 0.004$; $p = 0.024$; $p = 0.001$; $p = 0.009$, respectively; Figure 9).

Inflammation gradient

Variable number of polymorphonuclear cells and monocytes were found in the capsule formed around silicone block. Although inflammation gradient was more severe in group 3 and 4, no significant differences were observed regarding the intensity of capsule inflammation among the groups ($p = 0.093$; Table 2; Figure 10).

Vascular density

There was statistically significant difference in terms of vascular proliferation ($p = 0.014$). There was mild vascular density in 85.7% of groups 1 and 2, with no severe proliferation seen in these groups. On contrarst, 37.5% of group 3 and 25% of group 4 had severe vascular proliferation (Table 3; Figure 11).

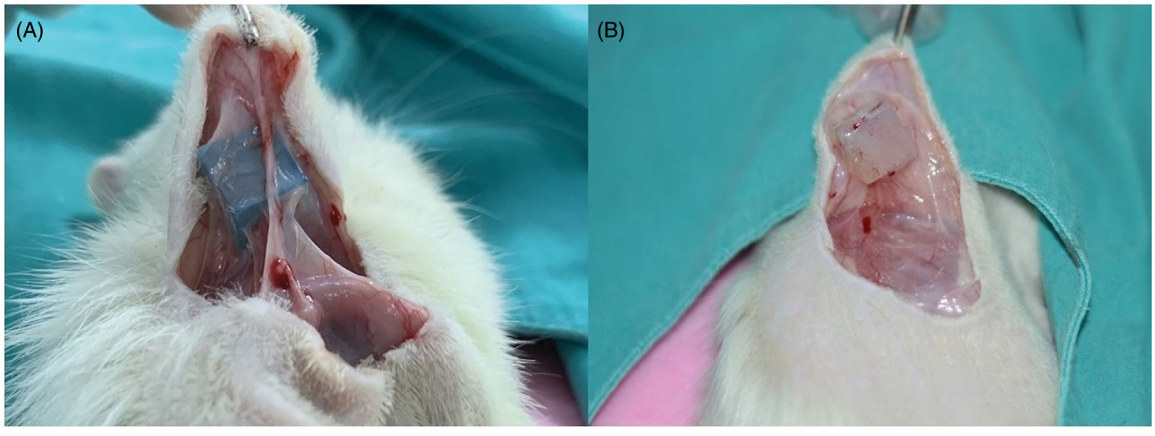

Figure 6. Adhesion of capsule to the surrounding tissues seen on explantation. (A) Group 2, (B) group 3.

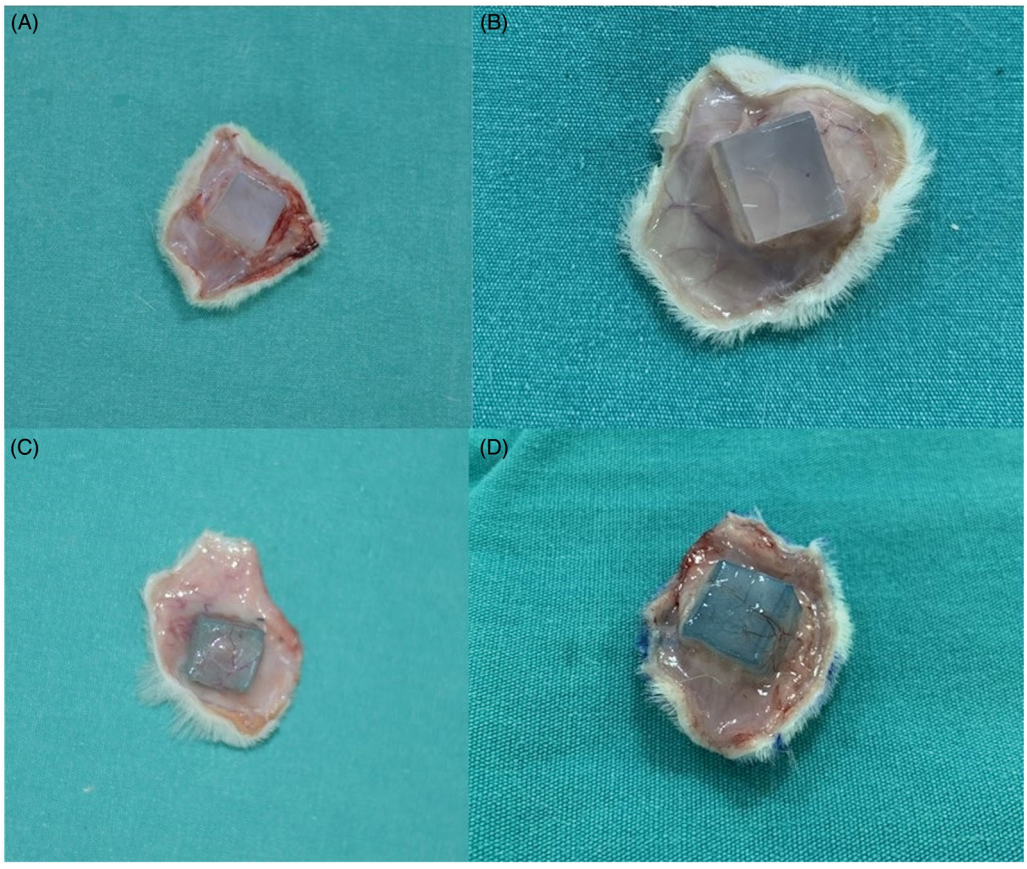

Figure 7. Macroscopic view of the capsule. (A) Group 1, (B) group 2, (C) group 3, (D) group 4.

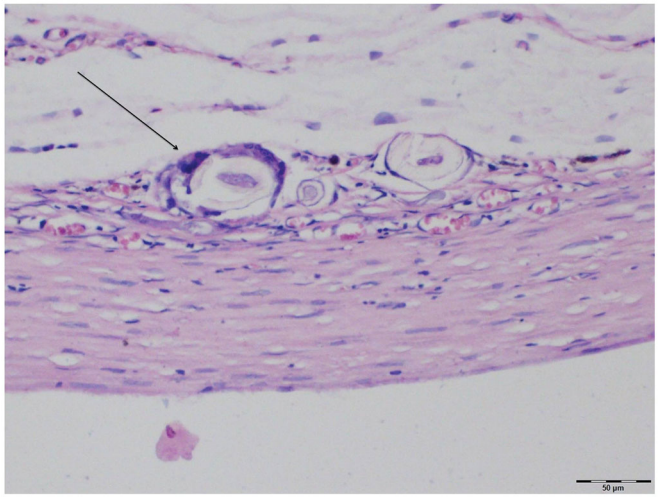

Figure 8. Methylene blue stained silicone particles withing capsular tissue (H&E staining, original magnification ×200).

Fibrosis gradient

An increased collagen density was observed by means of semi-quantitave analysis of Masson trichrome staining samples in groups 3 and 4 (Figure). There was statically significant differences among the groups ($p < 0.001$). Severe fibrozis was seen in 75% of subjects in groups 3 and 4 with none observed in control groups (Table 4; Figure 12).

Table 1. Dorsal and ventral capsule thickness in each group.

	Dorsal thickness (μm)	Ventral thcikness (μm)	*p* Value
Group 1	56.65 (25.5–70.2)	48.15 (33.5–69.4)	0.398[a]
Group 2	51.9 (32.5–63.1)	45.1 (33.7–72.4)	0.866[a]
Group 3	105.5 (77.1–147.1)	83.43 (37.9–155.98)	0.051[a]
Group 4	89.33 (43.6–182.6)	80.6 (55.1–179.34)	0.263[a]

[a]Wilcoxon test: Median (Minimum – Maximum).

Discussion

Capsular contracture is the most common long-term complication seen in alloplastic breast reconstruction. Several experimental and clinical studies using different pharmacological agents have been conducted in the aim of preventing or decreasing the incidence of capsular contracture. So far, no reports exist in scientific literature on the effect of MB on CC. In this study, we report on the development of CC in animal groups receiving peri-implant instillation of MB.

Unlike other published studies regarding the prevention of CC, our study is unique for capsular contractures in the scenario of immediate breast reconstruction. MB was instilled at the time of implant insertion. To imitate the exact clinical scenario of SLNB in the setting of immediate breast reconstruction with implant, MB had to be injected subdermally in the experiment as well. However, side effects of subdermal injection of MB are reported in the literature and were witnessed frequently in our clinical practice as well. Skin necrosis, wound dehiscence and implant exposure are among reported complications [6,10]. To avoid these advert events that may interfere with the outcome, we decided

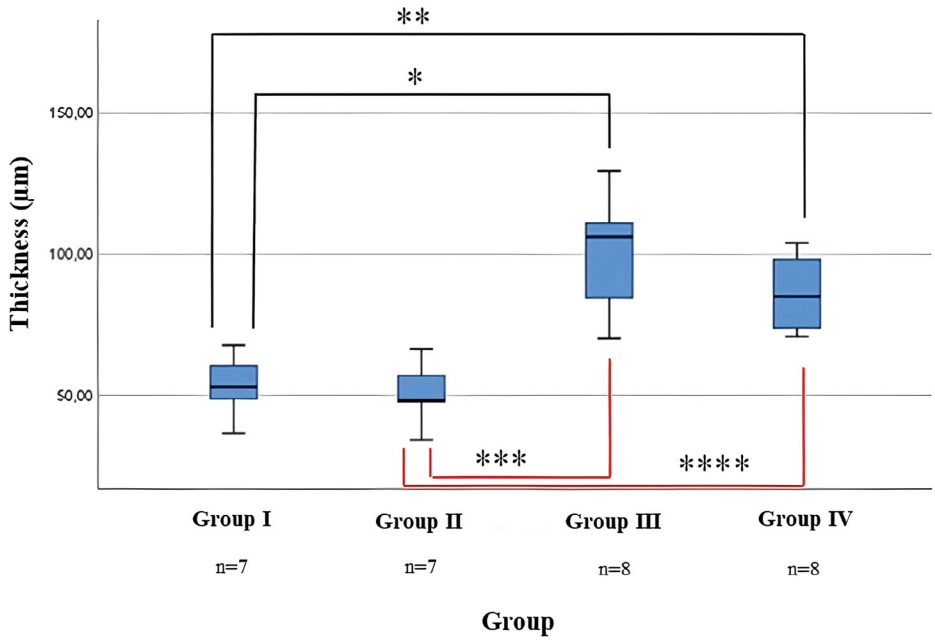

Figure 9. The average of capsular thicknesses for each group. *The difference between group 1 and 3 is statistically significant ($p = 0.004$), **The difference between group 1 and 4 is statistically significant ($p = 0.024$), ***The difference between group 2 and 3 is statistically significant ($p = 0.001$), ****The difference between group 2 and 4 is statistically significant ($p = 0.009$).

Table 2. Outcomes for inflammation severity.

	Group					
Inflammation	1	II	III	IV	Total	*p* Value
Mild	4 (57.1%)	5 (71.4%)	1 (12.5%)	1 (12.5%)	11 (36.7%)	**0.093**[a]
Moderate	3 (42.9%)	2 (28.6%)	4 (50.0%)	5 (62.5%)	14 (46.7%)	
Severe	0 (0.0%)	0 (0.0%)	3 (37.5%)	2 (25.0%)	5 (16.7%)	
Total	7 (100%)	7 (100%)	8 (100%)	8 (100%)	30 (100%)	

[a]Fisher-Freeman-Halton Exact Test.
There was no statistical significance among the groups ($p = 0.093$).

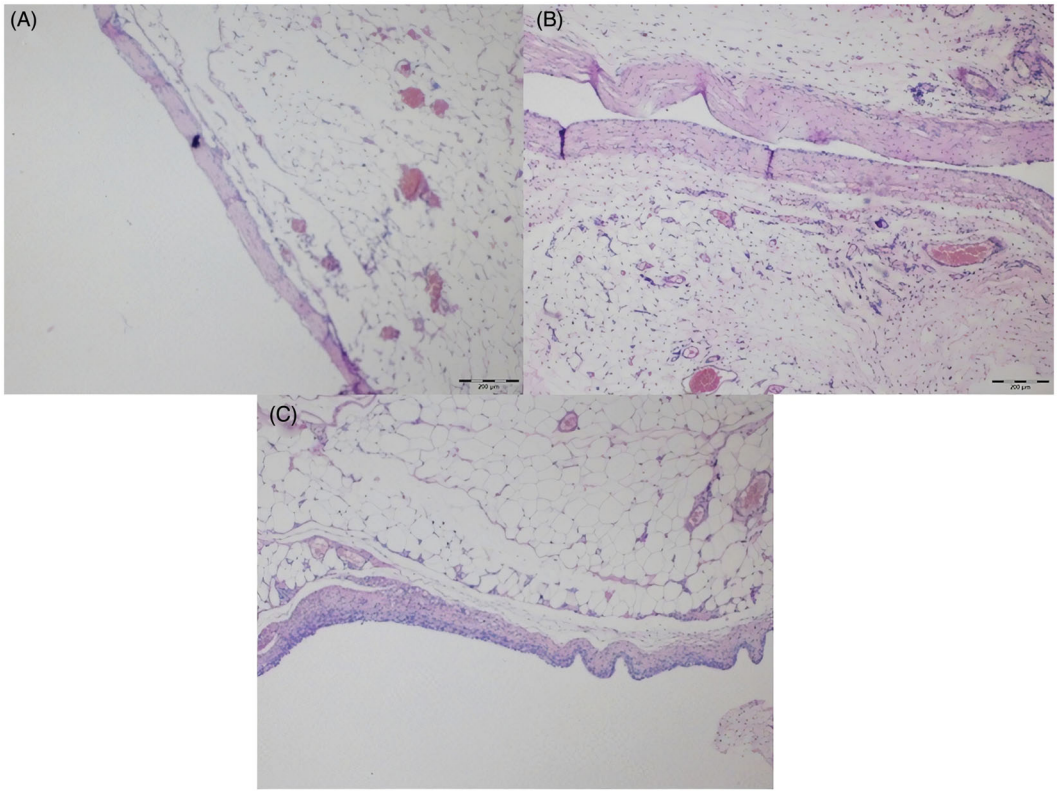

Figure 10. Different degrees of inflammation of a sample from group 3. (A) Mild, (B) moderate, (C) severe (H&E staining, original magnification ×40).

Table 3. Outcomes for vascular proliferation.

	Group					
Vascular proliferation	I	II	III	IV	Total	*p* Value
Less than 10	6 (85.7%)	6 (85.7%)	1 (12.5%)	2 (25.0%)	15 (50.0%)	**0.014**[a]
Between 10 and 20	1 (14.3%)	1 (14.3%)	5 (62.5%)	5 (62.5%)	12 (40.0%)	
More than 20	0 (0.0%)	0 (0.0%)	2 (25.0%)	1 (12.5%)	3 (10.0%)	
Total	7 (100%)	7 (100%)	8 (100%)	8 (100%)	30 (100%)	

[a]Fisher-Freeman-Halton Exact Test.
There was a statistical significance between the control and experimental groups ($p = 0.014$).

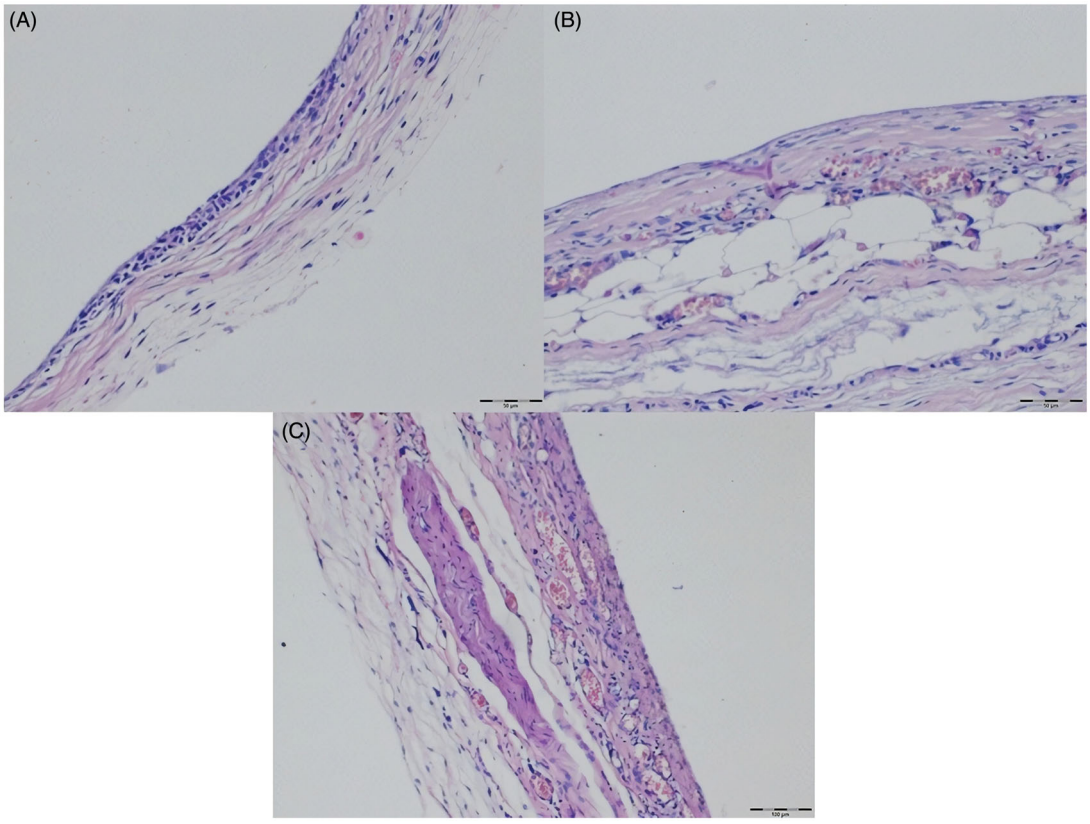

Figure 11. Different degrees of vascular proliferation of a sample from group 3. (A) Mild, (B) moderate, (C) severe (H&E staining, original magnification ×200).

Table 4. Outcomes for fibrosis gradient.

	Group					
Fibrosis	I	II	III	IV	Total	*p* Value
Mild	3 (42.9%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	7 (23.3%)	**<0.001**[a]
Moderate	4 (57.1%)	3 (42.9%)	2 (25.0%)	2 (25.0%)	11 (36.7%)	
Severe	0 (0.0%)	0 (0.0%)	6 (75.0%)	6 (75.0%)	12 (40.0%)	
Total	7 (100%)	7 (100%)	8 (100%)	8 (100%)	30 (100%)	

[a]Fisher-Freeman-Halton Exact Test.
There was a statistical significance between the control and experimental groups ($p < 0.001$).

to instil MB in the pocket rather than injecting it subdermally. This method provides the same interaction of MB with silicone implant that is seen in subdermal injection of the dye. In our clinical practice of SLNB where MB was injected subdermally, blue staining of silicone implants was noted in cases where the implant was explanted for various reasons (Figure 13). This shows that both subdermal and intra-pocket injection of MB lead to a remarkable dye exposure significant enough to initiate an inflammatory response.

In the literature, different durations of follow-up were published ranging from 4 weeks to 6 months [11–14]. In this study, all assessments were performed 60 days after surgery. Similar to previous studies and based on the fact that one month of rat's life coincide with 1.1 year of that of humans, the observation time of 60 days was enough to study CC in our work. In another word, this period coincides with 2 years follow-up in human beings through which most of clinically visible CC occurs.

Thickness of the capsule is correlated to the degree of CC [15]. Since inflammatory response to silicone implants is not uniform, these focal changes in cellular reactions are responsible for different collagen alignment and capsular thicknesses. Siggelkow et al. [16] have found thicker capsule in the posterior aspect of implants compared to anterior surface. In our study, there was no significant difference in terms of capsular thicknesses between

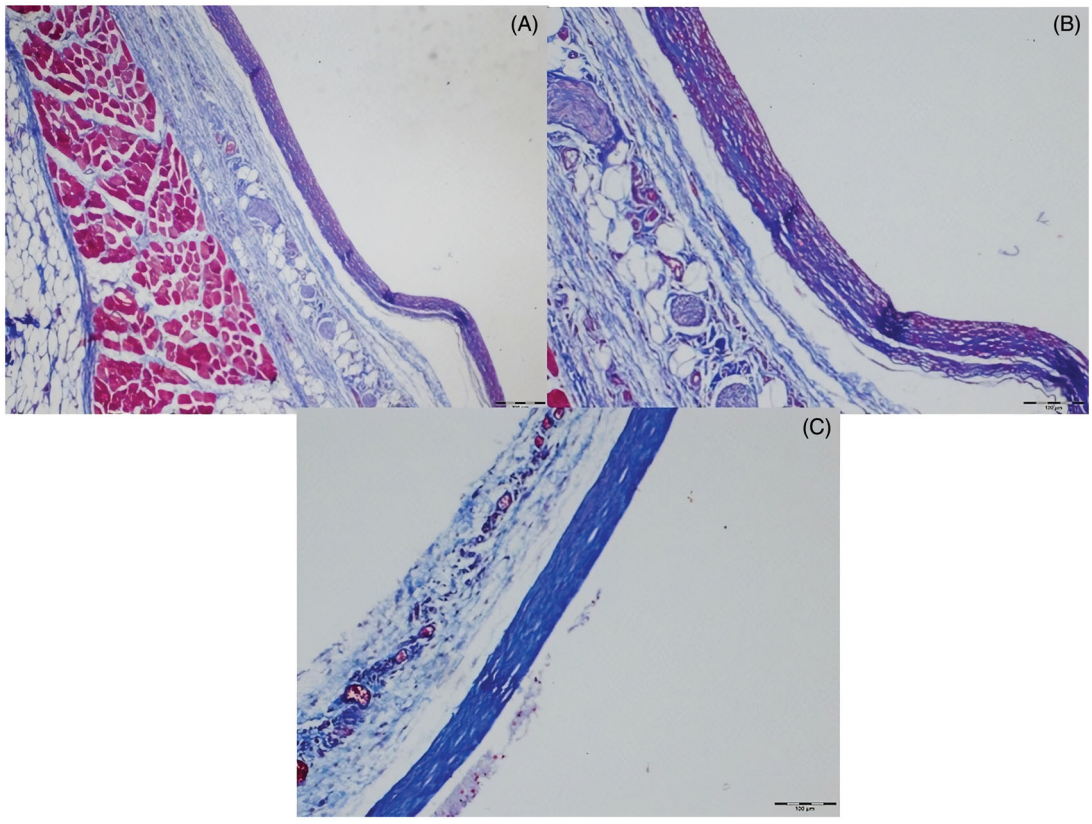

Figure 12. Different degrees of fibrosis of a sample from group 3. (A) Mild, (B) moderate, (C) severe (Masson trichrome staining, original magnification ×40).

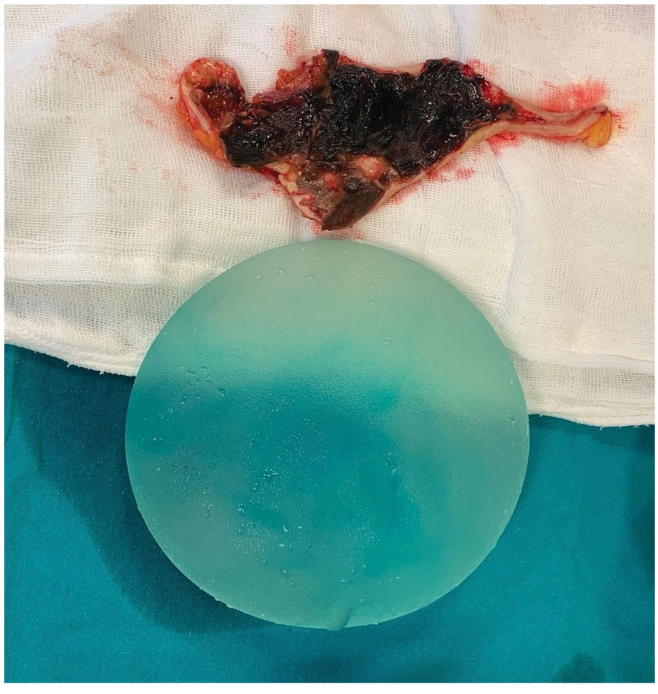

Figure 13. A picture showing methylene blue stained silicone implant extracted 3 months after breast reconstruction with breast skin flap necrosis due to intradermal injection of MB.

ventral and dorsal surfaces in the same group. However, a statistically significant difference was seen in terms of capsular thickness among groups with thicker capsules in study groups 3 and 4. Capsular thickness is generally accepted as an appropriate method to examine CC [17]. However this parameter is not sufficient to prove CC, additional histological examinations are required to prove the fibrotic state of the capsule formed.

Inflammation phase is an essential stage of wound healing. Different experimental studies in rodents discuss the importance of the body's inflammatory response in the pathogenesis of CC. The negative effect of MB on wound healing is discussed in the literature. Lane KL et al. [18] have studied the histological findings of tissues injected with MB. Ischemic ulceration, fibrinoid necrosis, inflammation and fibrosis was reported. In our study, although there were no significant differences in inflammation density among groups, severe inflammation was seen in study groups (3 and 4) compared to the control group. In addition to these findings, the staining of MB was observed around implants, inside capsular tissue and in surrounding tissues at the end of the study. Besides, MB stained silicone particles were seen in the inner layer of capsular tissue facing the silicone block. The persistence of this dye, in addition to silicone particles, may be responsible for prolonged inflammation and foreign body reaction leading to chronic inflammation and thereby hypertrophic scar formation instead of normal scar tissue.

Vascular intensity affects the degree of capsular contracture. An increase in vascularization causes increased capsular thickness by increasing the degree of fibrosis. Kim et al. [8] with the objective of examining the effect of Botulinum toxin-A on capsular contracture, reported a statistically significant difference regarding vessels count between control and study groups. Similarly, we have found a significant increase in vascular proliferation in study groups 3 and 4. The increased capsular thickness in these two groups can be explained by increased vascularity independent on the degree of inflammation or fibrosis. At this point, antigenic markers like CD31, CD34, CD133 or CD105 could have been used in determination of precise vessel count.

This mechanism of CC is initiated as a cellular response to an implant leading to progressive collagen formation. Also, fibroblasts responsible for collagen synthesis have been linked to capsular formation. Brazin et al. [19] have reported a positive relation between the quantity of fibroblasts in the capsular tissue and Baker's classification. The orientation and organization of collagen fibres are related to the severity of CC [16]. There are several studies supporting the effect of MB on fibrosis formation. A study by Mahdy et al. [20] has confirmed an increase in the degree of fibrosis after abdominal surgeries as 5 and 9% of MB is given intra-abdominally. In a similar study, Prien et al. [21] have reported adhesion formation in rats following an intraperitoneal injection of 9% MB. This effect was linked to the inflammatory reaction caused by macrophage activation. In the current study, tissue sections were stained with masson trichrome to evaluate the changes in collagen fibres, thereby the degree of fibrosis. There was a significant difference regarding fibrosis gradient among groups ($p < 0.001$). An injection of 0.1 ml of MB in group 3 had led to an expressive fibrosis in comparion to control group.

We originally hypothesized that changing the dose of MB would change the degree of CC. Brahma et al. [22] have studied the effective dose of MB in SLNB. They have showed that an injection of 5 ml of MB was associated with skin necrosis, yet this complication was not observed when the dose is reduced to 2 ml. Also, Zakaria et al. [23] have reduced the dose of MB in the objective of decreasing complications related to the dye. They have reported less inflammation with the use of a diluted dye in a ratio of 1:7. In our study, to evaluate whether an increased dose of MB is enhancing capsular formation or not, 0.2 ml of MB was given to subjects of group 4. There was no significant difference in terms of capsular contracture between group 3 and 4. Similar degree of inflammation, vascularization and fibrosis was seen in both groups. These data did not support our hypothesis and showed that increased dose of MB is not affecting the degree of CC.

The limitation of our study includes the lack of molecular parameters in collagen and myofibroblast detection and immunohistochemical parameters for vascular count. Relative biomarkers may have been used to gain insight into the inflammatory process. Longer duration of follow-up may be necessary to study long-term effect of MB on CC. We think that MB is enhancing CC by its toxic effect, initiating an inflammatory response leading to progressive fibrosis. This instillation of MB around silicone implants could be an inexpensive alternative animal model for capsular contracture research. Possible future studies are needed to determine the exact mechanism and the cellular level by which MB is causing CC. Also its effect on implant integrity should be examined as well.

In conclusion, this study points to the potential correlation between peri-implant staining by MB and capsular contracture. In this case, the degree of contracture is independent on the dose given. The impact of this study can be translated into clinical application by preference of other methods for sentinel lymph node detection rather than MB in patients that are candidates for immediate alloplastic breast reconstruction.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Abbas Albayati http://orcid.org/0000-0003-2806-3006

Burak Ozkan http://orcid.org/0000-0003-3093-8369

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