A Comparative Study between Two Localization Methods for Breast Cancer Prior to Neoadjuvant Chemotherapy

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Abstract

Background: The key to surgical planning for breast conservative surgery (BCS) after neoadjuvant chemotherapy (NAC) is tumor localization. Tumor marking can be done using different methods.

Aim of Study: The objective of this study was to compare two localization methods before initiation of NAC; a new cost-effective method using sterile silver rods versus the standard commercial titanium clip to assess if this novel cheap technique can be popularized in low-resource countries.

Patients and Methods: This retrospective comparative study was conducted on breast cancer patients admitted to oncology centre Mansoura University between May 2018 and April 2021. All patients have received NAC followed by surgery as recommended by our multi-disciplinary team (MDT). All the patients had a primary operable solitary breast cancer. Forty breast cancer patients were included; divided into 2 groups; 20 patients had titanium clip (group 1) and the other twenty had silver markers (group 2) before starting chemotherapy.

Results: Median clinical tumor size was 4.65 ± 1.6 cm in group 1 and 4.3 ± 1.8 cm in group 2 (p=0.206). After NAC treatment, there were no statistically significant differences in both groups regarding clinical and pathological responses. Median pathological tumor size was 1.8 ± 1.4 cm in group 1 and 1.6 ± 1.2 cm in group 2 (p=0.671). Median excised breast volume was larger in group 2 (220 g) than group 1 (110g); p<0.001. There were no reported major complications in both groups. Marker visibility and excision were easy in both groups. There were no statistically significant differences when comparing margin status and local recurrence rate.

Conclusion: Marking the tumor marginsby sterile silver markers before initiation of neoadjuvant chemotherapy is comparable to the commercial titanium clip with much lower cost.

Key Words: Breast cancer localization – Silver marker – Wire localization – Conservative breast surgery.

Introduction

NEOADJUVANT chemotherapy (NAC) became an integral part of the multidisciplinary management for breast cancer and has a long history which goes back almost five decades [1]. Many advantages were proven for NAC such as decreasing the tumor size to enable conservative breast surgery (CBS), down staging of the axillay lymph nodes to permit sentinel lymph node biopsy in node positive patients, and allows in-vivo test of response to therapy [2].

Currently, surgery after NAC is crucial even if clinical complete response has occurred [3]. CBS following downsizing by NAC has been proven to be oncologically safe regarding local relapse and overall survival. However, selection criteria must be attained, and precise localization of the tumor site should be performed before surgery. In many times, identification of the tumor bed is extremely hard if no pre-treatment localization method was done and the surgeon becomes in a big problem when he is unable to localize the tumor bed and sometimes finds himself forced to choose between either unsafe CBS versus unnecessary mastectomy [4].

Thus, pre-therapy tumor localization became the standard in cases receiving NAC and prepared for CBS [5]. Universally, many pre-treatment localization methods wereapplied and studied. Tattoo inks, radioactive iodine seeds and metallic clips have been widely used. However, no standard approach has been proven [6].

This study aims at comparing the safety, accuracy and the cost-effectiveness between two localization methods in breast cancer patients before initiating NAC to perform safe CBS.

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Patients and Methods

This retrospective comparative study was conducted between May 2018 and April 2021. All patients have received NAC then underwent surgery according to our Multi Disciplinary Team (MDT) decision. Our study has been approved by the local institutional board with a number of R.22.10.1904.

Inclusion criteria: Include patients with unifocal operable breast cancer planned for CBS after NAC who had pre-treatment tumor localization either by commercial titanium clip (group 1) or by sterile silver rods (group 2) and had preoperative breast MRI. All cases gave informed written consent. Patients with mastitis carcinomatosis, multifocal lesions or metastatic disease were excluded from the study. Moreover, patients who had a stationary or progressive response to NAC were excluded from the study.

Initial assessment:

All cases had conventional history taking and clinical examination for exact tumor location, skin affection, possibility of multicentricity and lymph node status. All cases had undergone a tru-cut needle biopsy, with histological and immunohistochemical (IHC) staining for ER, PR, HER2, and Ki67. Imaging of the breast was done initially by sono-mammography with or without breast MRI. Routine metastatic work up was done. Prechemotherapy routine laboratory investigations (CBC, liver functions, renal functions, ...etc) and echocardiography were performed. According to our MDT decisions, the patients were planned for NAC followed by CBS depending on the tumor/breast ratioand the biological subtyping.

Tumor localization prior to neoadjuvant therapy by commercial titanium clip (group 1):

Under ultrasonography (US) guidance, the radiologist inserted the titanium clip marker (Ultra-Mark) in the core of the tumor (Fig. 1). A post procedural mammogram was done in each patient to confirm correct placement of the clip inside the tumor (Fig. 2).

Tumor localization prior to neoadjuvant therapy by silver wire rods (group 2):

The tumor borders were marked by 3-5 radiopaque rods made from silver wire which was bought from the market as a roll of rude silver and designed to be one metre in length and 1mm in diameter. This roll was cut into small rods which are 2-3cm long and were sterilized by autoclave, then pocketed in a plastic sterile bag. One metallic rod was put at each border of the tumor (medial, lateral, upper, lower and posterior if possible). One metallic rod was loaded into a 20-gauge spinal needle, which was inserted through the skin after local anaesthetic injection. Our radiologist has propelled the spinal needle tip to reach one border of the tumor, under US guidance. The metallic rod was pushed with the needle's stylet when the spinal needle tip had touched the border. This was repeated for each border. To confirm correct placement of the markers, post-procedural mammogram was done (Fig. 3). The duration of the procedure in both groups was calculated.

Neoadjuvant therapy:

Our patients have received the standard protocolsbased on the biological type and as recommended by the medical oncology staff. CBC was performed before each cycle. The full course of the prescribed therapy regimens was given. After each cycle, the patients were examined and the response was recorded by clinical examination.

Clinical response and preoperative imaging:

Evaluation of clinical response was depending on breast imaging. Sono-mammography and breast MRI were done for all patients to assess residual disease extent and LN status after finishing the planned treatment. Response to treatment was categorized as complete, partial, stationary and progressive according to RECIST criteria (Response Evaluation Criteria in Solid Tumors). Timing between marker insertion and surgery was reported.

Surgery:

Following theneoadjuvant therapy, the patients have undergone surgery after at least 2 weeks from the last cycle to normalize CBC. Patients who attained criteria for breast preservation were listed for CBS. Patients who were not amenable for CBS were excluded from the study.

Tumor bed identification in group 1:

Preoperative, when the tumor became not detectable the radiologist inserted a metallic guide wire directed to the radiopaque titanium clip. The distance of the clip from the skin and distance of the clip from the tip of the guide wire were documented.

We have performed wide local excision (WLE) of the pathologic tissue guided by the residual palpable tumor, if present, or by the help of the guide wire which ends at the titanium clip in the tumor bed when the tumor has disappeared. The specimen was labelled, weighted and radiographed (to confirm removal of the clip) then sent for intraoperative frozen section examination (Fig. 4).

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Tumor bed identification in group 2:

Before surgery, when the residual lesion became invisible on imaging, the radiologist has relied on the metallic silver rods to localize the tumor bed and put a skin mark. During surgery, we have done (WLE) of the tumor bed by about 1cm wide of the palpated markers. We were usually able to palpate the markers in almost all cases and used them as a guide when performing the WLE. The specimen was labelled and weighted. Specimen mammography was done to confirm retrieval of all markers (Fig. 5). Intraoperative frozen section examination was used to confirm free safety margins. The operation time in both groups was recorded.



Fig. (1): (A): Titanium clip. (B): Technique of its insertion under US guidance. (C): Tip of the instrument reaching the core of the tumor.



Fig. (2): Mammogram after titanium clip insertion.



Fig. (3): (A) Silver wire roll cut into small rods. (B) Technique of marker insertion. (C) Post-procedural mammogram showing 3 silver markers at tumor margins.





Fig. (4): (A) PreNAC mammogram with titanium clip. (B) Post NAC mammogram achieving complete response with mammographic guide wire localization. (C) Intraoperative photo. (D) WLE specimen. (E) Specimen mammogram with the clip inside.

Follow-up for local recurrence and distant relapse:

The patients were followed-up for a median of 2 years (range: 1-4 years); every 3 months for the first year, and every 6 months for subsequent years.

Statistical analysis:

Data analysis was performed by SPSS software, version 18 (SPSS Inc., PASW statistics for windows version 18. Chicago: SPSS Inc.). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-normally distributed data and mean \pm Standard deviation for normally distributed data after testing normality using Shapiro Wilk test. Chi-Square was used to compare qualitative data between groups as appropriate. Student *t*-test was used to compare 2 independent groups for normally distributed data. Significance of the obtained results was judged at the $p \le 0.05$ level.



(A)

(B)





Fig. (5): (A) Preoperative skin marking at site of silver markers. (B) Pre-neoadjuvant therapy mammography showing 4 silver rods inserted at tumor margins. (C) Post-treatment mammography showing marked tumor regression with the markers in place. (D) Silver marker detected intraoperatively. (E) Lumpectomy specimen marked by threads. (F) Specimen mammogram with 4 markers inside.



Fig. (6): (A) Pre-treatment STIR image revealed hyperintense speculated solitary mass at lower outer quadrant of left breast (B) Post treatment post contrast study revealed tumor regression and small signal void.

Results

Forty patients with operable breast cancer received NAC and listed for CBS were included in our study. All patients had pre-treatment tumor localization; 20 patients had titanium clip (group 1) and 20 patients had silver markers (group 2). There were no statistically significant differences in age, BMI, pathological type and tumor stage between groups. The median age of the cases in group 1 was 43.5 years (range 26-74 years). The median age of cases in group 2 was 46.8 years (range 31-75 years). At diagnosis, 15 patients had stage II and 5 patients had stage III disease in group 1. Twelve patients had stage II and 8 had

Table (1): Patients and tumor characteristics.

stage III in group 2. Seventeen patients had invasive duct carcinoma (IDC) and 3 patients had invasive lobular carcinoma (ILC) in group 1. Eighteen patients had IDC and 2 patients had ILC in group 2. There was no statistically significant difference in the median clinical tumor size between groups; it was 4.65 ± 1.6 cm in group 1, and 4.3 ± 1.8 cm in group 2 (p=0.206).When comparing median excised breast volume of both groups, there was statistically significant difference. The median excised breast volume in group 1 was 110g (range 80-170g), however, it was 220g (range 100-300g) in group 2 (p=<0.001). The patients and tumor characteristics are provided in Table (1).

Characteristic	Titanium clip (group 1; n=20)	Silver markers (group 2; n=20)	<i>p</i> -value
Age/years (median, range)	43.5 (26-74)	46.8 (31-76)	0.428#
BMI (median, range)	28 (18-44)	26 (19-38)	0.297#
Median initial tumor size/cm (median, range)	4.65 (2.8-6.58)	4.3 (2.6-5.8)	0.206#
Mean excised breast volume/g (median, range)	110 (80-170)	220 (100-300)	<0.001 *#
Pathological type (trucut biopsy) n (%):			
IDC	17 (85.0)	18 (90.0)	<i>p</i> =1.0##
ILC	3 (15.0)	2 (10.0)	
Biological type (by IHC) n (%):			
Luminal A	8 (40)	6 (30)	0.507##
Luminal B	5 (25)	4 (20)	0.705##
HER 2 enriched	3 (15)	3 (15)	0.695##
Triple –ve	4 (20)	5 (25)	0.705##
Stage at diagnosis n (%):			
Stage II	15 (75)	12 (60)	0.311##
Stage III	5 (25)	8 (40)	

BMI: Body mass index. IHC: Immunohistochemical analysis. Used tests: # Mann Whitney U test. ##: Chi-Square test. *Statistically significant.

Before initiation of therapy, titanium clip was easily placed in the core of the tumor under US guidance within 3 minutes on average in group 1. No complications were reported. In group 2, sterile silver rods were put in all cases with median number four (range 3-5) prior to NAC. The procedure has taken 8 minutes on average. No patient complained of pain after one day of marker insertion.

After completion of the treatment course, there were no statistically significant differences in clinical and pathological responses between groups; 16 patients (80%) reported partial clinical response, and 4 patients (20%) reported complete clinical response (of whom 2 patients had achieved PCR at final pathology) in group 1. On the other hand, 17 patients (85%) reported partial response and 3 patients (15%) reported complete response (of whom 2 patients had achieved PCR) in group 2. There was no statistically significant difference in the median pathological tumor size between groups: it was 1.8 ± 1.4 cm in group 1, however; it was 1.6 ± 1.2 in group 2 (p=0.671). Clinical and pathological responses are provided in Table (2).

On preoperative assessment, markers were easily detected by sono-mammography in all cases without any reported migration in both groups. On breast MRI, the residual lesions, if present, were clearly described in all cases despite marker artifact in group 2 that did not represent a major drawback to our radiologists (Fig. 6).

Four patients in group 1, who achieved complete clinical response (CCR), had metallic guide wire localization the day before operation. Three patients in group 2, who achieved CCR, had skin marks the day before operation.

Clinical response	Titanium clip (n=20)	Silver markers (n=20)	р
Complete clinical response Partial clinical response	4 (20%) 16 (80%)	3 (15%) 17 (85%)	0.677##
Pathological response: PCR Partial pathological response Mean pathological tumor size/cm (median, range)	2 (10%) 18 (90%) 1.8 (0-3.3)	2 (10%) 18 (90%) 1.6 (0-3.2)	1.0## 0.671 #

Table (2): Clinical and pathological responses to NAC.

Used tests: #: Mann Whitney U test. ##: Chi-Square test. *Statistically significant.

All patients had undergone CBS:

In group 1, we were able to do WLE guided by the residual palpable tumor in 16 cases and by the help of the guide wire that ends at the titanium clip in 4 cases. Specimen mammogram revealed removal of titanium clip in all cases from the first time. In group 2, we were able to do WLE with 1cm gross wide margins guided by the silver markers placed at the tumor borders which could be easily palpated in almost all cases. Specimen mammograms revealed removal of all markers in 18 cases from the first time. The other two cases required re-excision to assure removal of all markers. Timing between marker insertion and surgery, mean operative time and other clinical and economic considerations are provided in Table (3).

Table (3): Clinical and economic considerations.

We did not report any major marker related complications in both groups. Two patients complained of feeling discomfort owing to the superficially palpated markers in their breasts in group 2, and their complaints were easily addressed. No patient had infection, allergy, migration or marker extrusion (Table 4).

Among the forty cases, only two had persistent infiltrated margins at frozen section examination; one from each group and they had converted to mastectomy. During follow-up period which ranged from 1 to 4 years (median 2 years), only two patients had ipsilateral local recurrence: One from each group. We did not report any distant relapse (Table 5).

	Group 1 (n=20)	Group 2 (n=20)	р
Duration of procedure/min	3.1±0.25	8.2±1.15	0.001 *!
Timing between marker insertion and surgery/weeks	16.12±2.3	18.35±2.56	0.006*!
Pre-operative marker visibility on imaging	20 (100%)	20 (100%)	1.0##
Operation time/min.	70.36±12.58	90.58 ± 10.56	0.001 *!
Removal of markers from the first time	20 (100%)	18 (90%)	0.487##
Rate of mastectomy conversion	1 (5.0%)	1 (5.0%)	1.0##
Cost/one patient (LE)	3000±120.59	40 ± 10.5	<0.001 *!

Used tests: ! Student t-test. ##: Chi-Square test. *Statistically significant.

Table (4): Complication rate (N=40).

	Group 1 (n=20)	Group 2 (n=20)	р
Migration	0	0	1.0
Allergy	0	0	1.0
Infection	0	0	1.0
Significant Pain	0	0	1.0
Feeling discomfort	2 (10%)	0	0.487

Table (5): Follow-up (N=40).

Median follow-up (2 years) (range: 1-4 years)	Group 1 (n=20)	Group 2 (n=20)	р
Local relapse	1 (5%)	1 (5%)	1.0
Distant relapse	0	0	1.0

Discussion

Primary systemic therapy isone of the essential lines of treatment for breast cancer patients. The response to NAC is imagistic in several cases, and the rate of pathological complete response (PCR) was reported to be as high as 32.9% in some studies [6]. Unfortunately, a good response to NAC may make recognition of tumor site extremely hard on post therapy imaging studies and thus accurate

localization and optimal CBS may be difficult [7,8,9]. In this situation, identification of tumor bed is almost impossible if a breast tissue marker was not previously placed [10].

CBS after NAC is safe regarding local relapse and overall survival. However, to achieve successful CBS, the true tumor bed should be wholly excised [11]. In fact, safe CBS following NAC is sometimes uncertain because of difficult recognition of the tumor bed by clinical exam and imaging tools after the tumor has shrunken. Therefore, localizing the tumor site prior to neoadjuvant therapy became standard to do successful CBS [12].

Up till now, there is no standard approachto localize the breast tumors before starting neoadjuvant treatment [13]. Several tumor localization methods were described. The tools used for labelling lesions in clinical practice include tattoo ink, metallic clips, charcoal suspension, magnetic implants and radioactive iodine seeds [14]. Skin tattoos are cheap and fast technique, but it is less precise [15]. Another technique is the intratumoral injection of charcoal. Intraoperative, the area of concern is visually recognized by the dark color on the patients' skin. Color migration and the risk of confusing the charcoal suspension with the tumor architecture on pathological analysisare major drawbacks [16]. Radioactive iodine seeds can also be used. It is an excellent technique, but it needs much safety regulations [17]. Then, the direct intralesional insertion of the magnetic implants is another effective method for tumor marking before NAC [18]. Actually, the use of commercial titanium clips is the most common method routinely applied by the clinicians.

In practice, the response to NAC is variable and sometimes unpredictable. Thus, the insertion of a breast tissue marker became standard [19]. Usually, to bypass another setting for clipping, placement of the commercial breast marker is done in the same setting of core needle biopsy. There are many kinds of titanium clips in the market produced by many companies [20]. Surprisingly, one commercial titanium clip costs about 3000 LE that is considered too expensive and cannot be popularized in Egyptian oncology centers.

In this study, we have used small radiopaque silver rods placed at the tumor borders using the 20 gauge spinal puncture needle to localize tumor bed before NAC. We have compared this novel cheap technique to the standard commercial titanium clip. The procedure of silver marker insertion was easy and not time consuming taking less than 10 minutes. It is considered a safe technique as silver rods have been autoclaved and inserted under complete aseptic conditions.

Many studies have been published to find an alternative to the high-cost commercial breast markers and revealed that the inexpensive metallic markers are good for tumor marking and do not interfere with post treatment imaging modalities [21,22,23].

Aggar wal et al. (2008) studied the feasibility of CBS in cases with large sized breast cancer using radiopaque silverrods to localize tumor margins before NAC [5]. They have used the same method of our study, however, the insertion of metallic markers was done by palpation without US guidance. They reported that these silver rods are cost-effective and safe.

Migration is one of the anticipated drawbacks of silver rods placement. The low resistance of normal breast tissue can permit silver markers to displace from their original site; however, rods were carefully inserted into the margin of the tumor with its half inside it. Therefore, the susceptibility of marker displacement is low because of the higher tumor tissue resistance [17]. We did not report any case with marker migration as revealed in post therapy imaging assessments and post excision specimen mammographies. Moreover, we did not report other complications like infection, allergy, or significant pain.

Several trials have shown that metallic markers are important for tumor marking and do not disturb the post therapy imaging studies including MRI [24-27]. We were able to evaluate tumor response to treatment and confirm marker location using multimodal imaging tools in both groups. The silver rods were detected as a radiopaque linear density on mammography, and as a hyperechoic linear structure on ultrasound. Although it is agreed that breast MRI is better than sono-mammography in post NAC tumor assessment [27,28], radiopaque markers may cause artifacts on post contrast studies according to marker quality and magnetic susceptibility [28]. In our study, the silver rods produced a small signal void on MRI images; however, the remaining tumor was precisely assessed on MRI without difficulty.

In our study, even when the carcinoma has achieved complete clinical response, we couldrecognize the tumor bed before surgery by imaging studies. We have excised the whole tumor bed, involving all pathologic tissue by the help of the guide wire which pointed to the titanium clip in group 1 and by the help of skin mark placed at the site of silver markers in group 2. These markers were easily palpated and removed during surgery.

We have used silver wire roll of about 1mm in diameter that can be cut into small pieces and sterilized in the autoclave. Comparing to the commercial titanium clips, the silver rods have much lower cost, and the length could be adjusted so as to be easily felt in breast during CBS. The cost of this novel technique is about 40 LE. versus 3000 -4000 LE for the commercial titanium clip. The possible complications such as migration, infection, allergy and intolerable pain were not reported in any of our patients. Two patients complained of feeling discomfort because of the superficially placed markers and their concerns were easily managed conservatively.

The duration of the procedure of marker insertion, operation time, and median excised breast volume were significantly different between both groups. Regarding the duration of the procedure, it was logic to take a few more minutes to insert 4 markers (on average) at tumor margins in group 2. We will try to study the feasibility of insertion of one silver marker in the core of the tumor in the next publication. Regarding the operation time, we took a little extra-time to carefully detect the silver markers by palpation so as not to miss any marker in the specimen photograph. When comparing the median excised breast volume, it was larger in the silver marker group because we have planned our resection margins to be wider than the palpated markers at the tumor margins incorporating the all markers in the resected specimen. On the contrary, we have planned our resection margins in the titanium clip group to be directed to the clip in the tumor core. However, these larger excised volumes, as stated in literature [27,28,29] did not translate into better oncologic outcomes. The rate of positive safety margins and local recurrence were the same between both groups.

Some limitations in our study can be discussed. First, It is a retrospective study and only patients that had pretreatment tumor localization, preoperative MRI and listed for CBS were included. So, a selection bias may be present. Second, the small number of cases which limited to 40 patients cannot permit for standardization of our results. Third, we have a relatively short period of follow-up for local recurrence within a median of 2 years.

Conclusion:

Using sterile silver rodsfor breast cancer localization prior to neoadjuvant therapy is comparable to the commercial titanium clips with much lower cost. It issafe, easy, and practical with low complication rate. Further studies are needed to refine this new technique and achieve better results.

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دراسة مقارنة بين طريقتين لتحديد مكان الورم في مرضى سرطان الثدى قبل بدء العلاج الكيماوي الأولى

المقدمة : حجر الأساس فى التخطيط الجراحى للأستئصال التحفظى للثدى بعد العلاج الكيماوى هو تحديد مكان الورم. هناك العديد من الطرق المستخدمة لعمل هذا الإجراء.

الغرض من البحث : المقارنة بين نوعين من طريق تحديد الورم قبل بدء العلاج الكيماوى. طريقة جديدة ذات طابع اقتصادى وهى استخدام عيدان الفضة المعقمة والطريقة المعروفة باستخدام مشبك من التيتانيوم ومعرفة إمكانية استخدام الطريقة الجديدة الاقتصادية على نطاق واسع فى الدول النامية.

طريقة البحث : دراسة مقارنة أجريت بأثر رجعى على حالات أورام الثرى بمركز أورام المنصورة فى الفترة من مايو ٢٠١٥ إلى أبريل ٢٠٢٢ . كل الحالات تلقت العلاج الكيماوى ثم خضعت للجراحة حسب توصيات اللجنة العلمية بالمركز . أربعون حالة تمت دراستها تم تقسيمها إلى مجموعتين عشرون تم تحديد الورم باستخدام عيدان الفضة المعقمة. وعشرون باستخدام مشبك التيتانيوم قبل بدء العلاج الكيماوى.

النتائج : الرقم الوسيط لحجم الورم إكلينيكياً كان 4.65±1.6 سم فى المجموعة الأولى و4.3±1.8 سم فى المجموعة الثانية. بعد بدء العلاج الكيماوى لم يكن هناك فرق بين المجموعتين من حيث الاستجابة الكلية والجزئية للعلاج سواء بالفحص الإكلينيكى أو بالأشعة . وأظهرت النتائج أنه لا يوجد فرق بين المجموعتين من حيث حدوث مضاعفات. رؤية محدد الورم وعمل الاستئصال تم بسهولة فى المجموعتين. ولم يكن هناك فرق فى حالة حزام الأمان أو معدل ارتجاع الورم.

الاستتتاج : استخدام عيدان الفضة المعقمة فى تحديد مكان أورام الثدى قبل بدء العلاج الكيماوى طريقة آمنة وسهلة وعملية واقتصادية. وليس لها أعراض جانبية ولا تسبب آلم للمريض ويمكنها مجارة استخدام مشبك التيتانيوم ولكن بتكلفة أقل.