Efficacy and safety of a bridging strategy that uses intravenous platelet glycoprotein receptor inhibitors for patients undergoing surgery after coronary stent implantation: a meta-analysis

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Abstract

Background: Current guidelines indicate we can consider a bridging strategy that uses intravenous, reversible glycoprotein inhibitors for patients that required surgery following recent stent implantation. However, no strong clinical evidence exists that demonstrates the efficacy and safety of this treatment. Therefore, in this study, the efficacy and safety of a bridging strategy that uses intravenous platelet glycoprotein receptor inhibitors will be evaluated.

Methods: A meta-analysis was performed on preoperative bridging studies in patients undergoing coronary stent surgery. The primary outcome was the success rate of no major adverse cardiovascular events (MACE). The secondary outcomes were the success rate of no reoperations to stop bleeding.

Results: A total of 10 studies that included 382 patients were used in this meta-analysis. For the primary endpoint, the success rate was 97.7% (95% CI 94.4–98.0%) for glycoprotein IIb/IIIa inhibitors, 98.8% (95% CI 96.0–100%) for tirofiban (6 studies) and 95.8% (95% CI 90.4–99.4%) for eptifibatide (4 studies). For secondary endpoints, the success rate was 98.0% (95% CI 94.8–99.9%) for glycoprotein IIb/IIIa inhibitors, 99.7% (95% CI 97.1–100%) for tirofiban (5 studies), and 95.3% (95% CI 88.5–99.4%) for eptifibatide (4 studies).

Conclusion: The results of this study showed that the use of intravenous platelet glycoprotein IIb/IIIa inhibitors as a bridging strategy might be safe and effective for patients undergoing coronary stent implantation that require surgery soon after.

Keywords: Antiplatelet therapy, Bridging therapy, Tirofiban, Eptifibatide, Surgery

Background

Current guidelines recommend that patients diagnosed with stable coronary artery disease with stent implants should receive dual antiplatelet therapy (DAPT) that uses a P2Y12 inhibitor and aspirin for 6 months and patients with acute coronary syndrome for 12 months unless they show contraindications such as bleeding [1–6]. However, approximately 5% of patients undergo surgery in the first year following their percutaneous coronary intervention (PCI) [7–9]. Dual antiplatelet therapy increases the intra and perioperative bleeding risk, and surgery is associated with pro-inflammatory and pro-thrombotic effects; therefore, increasing the risk of coronary thrombosis at...
the level of the stented vascular segment and throughout the coronary vasculature [10].

Recent guidelines indicate that intravenous antiplatelet drugs may be considered for perioperative bridging treatment. However, to the best of the authors’ knowledge, there is no strong clinical evidence that demonstrates the efficacy of bridging with either parenteral antiplatelet therapies [1, 3]. Therefore, in this meta-analysis, the efficacy and safety of a bridging strategy that uses intravenous platelet glycoprotein receptor inhibitors will be evaluated.

**Methods**

A systematic search was conducted to identify relevant studies within databases, such as PubMed (January 1, 1946, to November 15, 2020), EMBASE (January 1, 1974, to November 15, 2020), and the Cochrane Library (inception to November 15, 2020). As a result, the following keywords were used: antiplatelet therapy, aspirin, clopidogrel, ticagrelor, prasugrel, GP IIb/IIIa inhibitor abciximab, tirofiban, eptifibatide, and surgery.

Any experimental and observational studies were included except for case reports without any limits and language restrictions. These studies described the use of an intravenous antiplatelet bridging treatment strategy for patients with coronary heart disease that had a stent implanted within 6 months of when surgery was planned.

Two reviewers independently extracted the data and contacted the relevant authors to obtain detailed data when the information was not comprehensive. Disagreement was resolved through negotiation. In addition, when there was no consensus, a recommendation from a third reviewer was involved.

Finally, 18 evaluation checklists were formed based on improvements to the Delphi technology. They were used to evaluate the quality of the case series study methodology. Each study counted the total number of positive items based on the consensus of the reviewers. This methodological quality assessment checklist did not recommend using scoring methods but gave corresponding options for each item. If the study met 14 (70%) or more checklist parameters, it was considered acceptable.

The primary outcome of this meta-analysis was the success rate of no major adverse cardiac events defined by each study, such as myocardial infarction, stent thrombosis, cardiogenic shock, sudden cardiac death, and death. The secondary outcome was the success rate of no reoperation to stop bleeding as defined by each study. Statistical analysis was performed using Stata (Stata15, USA) software. To calculate the success rate of the bridging treatment, calculations were based on two aspects, avoiding major adverse cardiovascular events (primary endpoint) and avoiding reoperation due to bleeding (secondary endpoint). Cochrane Q statistic ($p$-values ≤ 0.1 were considered significant) and I² statistic (25%, 50%, and 75% were associated with low, medium, and high heterogeneity, respectively) were used to evaluate the heterogeneity between various studies. Publication bias was assessed using Egger’s test ($p < 0.1$). In addition, the sensitivity was evaluated to ensure the robustness of the results, and subgroup analysis was conducted after the bridge therapy drugs were separated (tirofiban and eptifibatide).

**Results**

The initial search yielded 582 unique studies for review (Fig. 1). Following the screening, a full-text review was conducted on 50 special reports. Finally, 11 studies were included in the qualitative synthesis. Out of 11 studies, 10 provided sufficient details for meta-analysis. The key characteristics and findings of the included studies, which included two prospective and eight observational studies, are given in Table 1. Other important details of each article are shown in Table 2.

This study included ten studies [11–20] with 382 patients. Among them, 6 studies [11, 12, 14, 16–18] included 215 patients that used tirofiban for bridging therapy. Four studies [13, 15, 19, 20] had 167 patients that used eptifibatide for bridging therapy.

MACE was reported in all studies included, while reoperation due to bleeding was reported in seven studies. Walker 2017 mentioned that four bleeding events occurred in all patients, three minimal TIMI bleeding, one minor TIMI bleeding, and only one required blood transfusion and drug discontinuation. The results of Polito 2018 suggested three cases of uncomplicated anemia in bridging patients after surgery. So we believed that there were no cases of reoperation due to bleeding in these studies and included them in the calculation. Reoperation due to bleeding might be considered the most objective safety endpoint because it does not depend on the different criteria adopted for bleeding transfusion. All studies included were supposed to be of acceptable quality according to the modified Delphi technique (Table 3) [21].
Among the 382 patients, 367 did not show any major adverse cardiac events, and the success rate was 97.7% (95% CI 94.4–98.0%). According to the results of six studies, the success rate of tirofiban was 98.8% (95% CI 96.0–100%). In addition, the success rate of eptifibatide was 95.8% (95% CI 90.4–99.4%) based on the results of four studies (Fig. 2a). The risk of publication bias appeared to be low ($p = 0.508$, 95% CI $0.391$ to $0.727$) (Fig. 3a). The findings were robust to sensitivity analyses performed for bias, study design, type of operation, and the variations in estimate modeling mentioned previously (Fig. 4a).

Because each study used a different definition of bleeding, and each patient underwent another kind of surgery, the risk of bleeding differed. Therefore, reoperation due to bleeding was considered the secondary endpoint of the study. Among the 382 patients, 369 did not record reoperation due to bleeding, and the
| References  | Country     | No. of patients | Age | Type       | Non-cardiac surgery(n) | Type of stents | Time from PCI to surgery (months) | Bridging protocol | Non-MACE Number | Success rate(95% CI) | Non-reoperation Number | Success rate(95% CI) |
|-------------|-------------|-----------------|-----|------------|------------------------|----------------|----------------------------------|-------------------|----------------|---------------------|------------------------|---------------------|
| Xia (2013)  | China       | 21              | 63  | Obs,Prosp  | 21(100%)               | DES            | 6                                | Initiated tirofiban 4.8 days prior to surgery; stopped tirofiban 4 h prior to surgery | 21              | 100% (83.9–100%)    |                     | 21                     | 100% (83.9–100%)    |
| Walker (2017) | USA        | 20              | 72  | Obs,Restrosp | 11(55%)               | DES            | 1.1                              | Initiated tirofiban 3.5 days prior to surgery; stopped tirofiban 5.4 h prior to surgery | 18              | 90.0% (68.3–98.8%)  | 20                     | 100% (83.2–100%)    |
| Savonitto (2010) | USA    | 30              | 65  | Obs,Prosp  | 21(70%)               | DES            | 4                                | Initiated tirofiban 4 days prior to surgery; stopped tirofiban 4 h prior to surgery | 30              | 100% (88.4–100%)    | 30                     | 100% (88.4–100%)    |
| Polito (2018) | Italy      | 21              | 62  | Obs,Restrosp | 0(0%)                 | DES            | 0,23                             | Initiated tirofiban 3 days prior to surgery; stopped tirofiban 4 h prior to surgery | 20              | 95.2% (76.2–99.9%)  | 21                     | 100% (83.9–100%)    |
| Marcos (2011) | Netherlands | 36              | 66  | Obs,Restrosp | 21(58%)               | Mixed(58%DES)   | 2.6                              | Initiated tirofiban 4 days prior to surgery; stopped tirofiban 4 h prior to surgery | 36              | 100% (90.3–100%)    | 35                     | 97.2% (85.5–99.9%)  |
| References     | Country | No. of patients | Age | Type          | Non-cardiac surgery(n) | Type of stents       | Time from PCI to surgery (months) | Bridging protocol                                                                 | Non-MACE Number | Success rate(95% CI) | Non-reoperation Number | Success rate(95% CI) |
|----------------|---------|-----------------|-----|---------------|------------------------|----------------------|-------------------------------|----------------------------------|---------------------|----------------------|--------------------------|----------------------|
| Servi (2016)   | Italy   | 87              | 67.4| Obs,Restrosp  | 59(68%)                | 91%                  | 3.4                          | Initiated tirofiban 3 days prior to surgery; stopped tirofiban 4 h prior to surgery | 85                  | 97.7% (91.9–99.7%)    | 87                       | 100% (95.8–100%)       |
| Waldron (2017) | USA     | 30              | 65  | Obs,Restrosp  | 30(100%)               | DES                  | Not mention                   | Used eptifibatide, not mention bridging details                        | 27                 | 90.0% (73.5–97.9%)    | 30                       | 100% (88.4–100%)       |
| Rassi (2012)   | USA     | 100             | 63.2| Obs,Restrosp  | 29(29%)                | Mixed(89%DES)        | 5.8                          | Initiated eptifibatide 5.3 days prior to surgery; stopped eptifibatide 7 h prior to surgery | 93                 | 93.0% (86.1–97.1%)    | 90                       | 90.0% (82.4–95.1%)     |
| Morrison (2012)| USA     | 19              | 65  | Obs,Restrosp  | 63(2%)                 | DES                  | 3.5                          | Initiated eptifibatide 2.6 days prior to surgery; stopped eptifibatide 10 h prior to surgery | 19                 | 100% (82.4–100%)      | 18                       | 94.7% (74.0–99.9%)     |
| Barra (2016)   | USA     | 18              | 61.9| Obs,Restrosp  | 13(72%)                | Mixed(89%DES)        | 3.5                          | Initiated eptifibatide 2.7 days prior to surgery; stopped eptifibatide 6 h prior to surgery | 18                 | 100% (81.5–100%)      | 17                       | 94.4% (72.7–99.9%)     |
success rate was 98.0% (95% CI 94.8–99.9%). According to the results from six studies, the success rate of tirofiban was 99.7% (95% CI 97.1–100%). The success rate of eptifibatide was 95.3% (95% CI 88.5–99.4%) based on the results of four studies (Fig. 2b). The risk of publication bias appeared to be low ($p = 0.11, 95\% \text{ CI} -0.227 \text{ to } 1.145$) (Fig. 3b), and sensitivity analysis was robust (Fig. 4b).

**Discussion**

This study showed that the use of glycoprotein IIb/IIIa inhibitors for bridging antiplatelet therapy might be safe and effective for patients undergoing coronary stent implantation that require surgery within 6 months and whose bleeding was classified as high risk. However, the intensive care unit must perform the bridging treatment with sufficient monitoring and testing conditions.

Glycoprotein IIb/IIIa are receptors on the surface of platelets that mediate the binding of fibrinogen, von Willebrand factor, and vitronectin to platelets, which cause platelets to cross-link and aggregate. Abciximab, tirofiban, and eptifibatide block this process in a targeted manner. Tirofiban and eptifibatide have a shorter action time, and their platelet inhibitory effect can last for 2–4 h following administration [22].
The previous studies [23] found that in patients with coronary heart disease that underwent non-cardiac surgery within 1 month of coronary stent implantation, the incidence of perioperative death, acute myocardial infarction, stent thrombosis, and other cardiac adverse events was as high as 30%; in 2 out of 6 of cases, surgery was performed at the end of the month, and the incidence of the previously mentioned adverse events decreased to 10–15%; after 6 months, the incidence of surgery decreased to <10%. Therefore, for patients with coronary stent implantation, if surgery with a high risk of bleeding is planned, it is necessary to carefully assess the advantages and disadvantages (e.g., the risk of cardiovascular complications that are caused by discontinuing antiplatelet drugs and the risk of bleeding caused by continuing drugs).

According to a multidisciplinary management opinion [24], in patients >12 months after PCI, the risk of perioperative thromboembolism was low, and therefore, elective surgery could be performed. In patients <12 months after PCI, the time for elective operation should be determined based on several factors. In summary, elective surgery should be performed ≥2 weeks after coronary artery balloon dilation, ≥1 month after implantation of a BMS, and ≥3 months after the implantation or elective surgery is performed again. For the new generation of DES, the time could be appropriately shortened based on the situation, and elective surgery should be performed ≥12 months after implantation of a bioabsorbable stent (BVS).

The risk of bleeding during the perioperative period is mainly affected by the type of surgery or the invasive nature of the procedure. In general, any long-duration (>45 min) surgery and surgery on vital organs (e.g., central nervous system and heart), blood-rich organs (e.g., liver and spleen), large blood vessels, active fibrinolytic sites (i.e., the urinary system) and
Fig. 2  a The forest map for non-MACE, b the forest map for non-reoperation
invasive procedures should be considered to have a high risk of bleeding [25, 26]. In patients treated with antiplatelet drugs before surgery, the PRECISE-DAPT score could be used to evaluate the patient’s risk of bleeding [27].

This study has two main limitations. First, the included studies were observational and were not randomized controlled experiments. Second, the included studies used a different definition of bleeding; therefore, only the success rate of freedom from reoperation without bleeding was included.

Conclusions

In patients that require surgery after recent stent implantation, a bridging strategy that uses intravenous platelet glycoprotein receptor inhibitors might allow the temporary discontinuation of dual antiplatelet drugs without increasing the risk of bleeding. The decision to perform bridging treatment and careful risk stratification of ischemic events and bleeding requires strict cooperation between surgeons, cardiologists, and anesthesiologists. Large-scale randomized clinical trials are needed to confirm this result further.

Abbreviations

MACE: Major adverse cardiovascular events; BMS: Bare-metal stent; DES: Drug-eluting stent; DAPT: Dual antiplatelet therapy; PCI: Percutaneous coronary intervention; BVS: Bioabsorbable stent.

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Authors’ contributions

FW: Data curation; Formal analysis; Investigation; Writing original draft. KM: Data curation; Formal analysis; Writing review & editing. RX: Project administration; Resources. BH: Software; Writing review & editing. JC: Supervision; Validation. ZZ: Supervision; Validation. YL: Software; Validation. MM: Funding acquisition; Methodology. All authors read and approved the final manuscript.

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Fig. 3  a The funnel plot for non-MACE. b the funnel plot for non-reoperation

Fig. 4  a The sensitivity analysis for non-MACE. b the sensitivity analysis for non-reoperation
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