Injury, Int. J. Care Injured 46 (2015) 954–962

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Is early hip fracture surgery safe for patients on clopidogrel? Systematic review, meta-analysis and meta-regression

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ARTICLE INFO

Article history:
Accepted 5 March 2015

Keywords:
Hip fracture
Clopidogrel
Antiplatelets
Blood transfusion
Mortality

ABSTRACT

Introduction: Hip fracture is a common presentation in the elderly population, many of whom will be taking the antiplatelet clopidogrel, which has the potential to increase perioperative bleeding. The aim of this systematic review and meta-analysis was to answer the questions: (1) is early hip fracture surgery for patients on clopidogrel associated with worse postoperative outcomes compared to patients not on clopidogrel? (2) is early versus delayed surgery for these patients associated with worse postoperative outcomes?

Methods: A systematic search was conducted of MEDLINE, EMBASE, Cinahl and AMED databases. Results from patients undergoing early surgery on clopidogrel were compared to a control group not taking clopidogrel. In addition, patients taking clopidogrel undergoing early and delayed surgery were compared.

Results: For patients taking clopidogrel undergoing early surgery, there was no associated increase in overall mortality (OR 0.89; 95% CI: 0.58–1.38) or 30-day mortality (OR 1.10 95% CI: 0.48–2.54). However, there was an associated increase in blood transfusion (OR 1.41 95% CI: 1.00–1.99). There was an associated decreased length of stay in the early surgery versus delayed surgery group (weighted mean difference −7.09 days (95% CI: −10.14 to −4.04).

Discussion: Early surgery appears safe for patients with hip fracture though there may be a small increase in the rate of blood transfusion. However, larger prospective trials are required to confirm these findings.

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Introduction

Hip fracture is a common presentation in elderly patients with a UK incidence of around 75,000 per year [1] and a 30-day mortality of around 8–10% [2,3]. In addition, hip fracture represents a significant financial healthcare burden to society [4]. There has been a three-fold increase in the number of hip fracture patients with co-morbid cardiovascular disease [5]. Many of these patients are taking anti-platelet drugs such as clopidogrel.

Clopidogrel is a thienopyridine, adenosine dinucleotide phosphate (ADP)-receptor antagonist [6] with an irreversible antiplatelet effect lasting around 7 days [7]. It has proven efficacy in the management of acute coronary syndrome [8], transient ischaemic attack, peripheral arterial disease, post-coronary artery bypass graft [9] and stroke [10]. However, the increased use of antiplatelet agents has the potential to increase bleeding and associated complications during surgery [11,12]. Furthermore, neuraxial anaesthesia whilst taking clopidogrel is not recommended [13], and 5 days of clopidogrel withdrawal is recommended to regain sufficient platelet function to safely perform the procedure [14] although risks associated with not withdrawing clopidogrel may be low [15].

However, cessation of antiplatelet therapy perioperatively may increase the risk of thrombotic events [16,17,18]. Current guidelines suggest surgery for hip fracture should occur the day of, or after fracture occurrence [1]. Indeed, delayed surgery for hip fracture is associated with increased mortality [19,20] and length of stay [21]. This presents a dilemma of whether to delay surgery to allow drug effects to subside or perform timely surgery to encourage early mobilisation and reduce mortality.

Cross sectional studies have identified wide variations in current clinical practice with regards to clopidogrel withdrawal before hip fracture surgery [22,23,24]. Most reports regarding clopidogrel are small, single centre studies, which do not allow meaningful conclusions to be drawn.

Therefore, the aim of this review was to address the following research questions: (1) is early hip fracture surgery for patients on clopidogrel associated with worse postoperative outcomes

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http://dx.doi.org/10.1016/j.injury.2015.03.024
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compared to patients not on clopidogrel? (2) is early versus delayed surgery for these patients associated with worse postoperative outcomes?

Materials and methods

This systematic review was conducted in accordance with the MOOSE checklist [25]. One of the investigators conducted the search (BD), which was updated in August 2014. Databases searched included MEDLINE (1946–2014), EMBASE (1980–2014), Cinahl (1981–2014) and AMED (1985–2014). Key words searched included 'Clopidogrel', 'Plavix', 'Platelet Aggregation Inhibitors', 'Ticlodipine' and 'Hip AND Fracture' (Appendix A). References and citing articles were searched to identify additional studies. Authors were contacted if further information was required.

Studies were included if they were (a) randomised controlled trials or (b) observational studies examining patients undergoing early hip fracture surgery who were taking clopidogrel on admission. Patients with both intra and extracapsular fractures were considered. Outcomes were determined a priori. These included mortality, transfusion requirements, infection (as defined in the studies, both composite and individual infectious complications as reported), wound haematoma, blood loss, bleeding volume, acute coronary syndrome, thromboembolic events, stroke, length of stay and reoperation. Where possible, data were used from patients on clopidogrel only and not on concurrent aspirin. Exclusion criteria included studies with cohorts of patients on other antiplatelet medication except aspirin, non-English language papers and letters or surveys.

Data were extracted onto an electronic database and included mean age, proportion of female patients, fracture type, cohorts compared, country, number of participants, study type, type of anaesthesia, concurrent aspirin and thromboprophylaxis use, timing of surgery and protocol on clopidogrel cessation. Study quality was assessed using the Newcastle–Ottawa scale [26]. Quality assessment was performed with investigators blinded to study outcomes. Each study was further examined for likely confounders between study groups that could bias results.

Where appropriate, formal meta-analysis was undertaken using Mantel–Haenszel odds ratios (OR) or weighted mean differences (WMD) presented with 95% confidence intervals. Heterogeneity was assessed using the I^2 statistic and Cochran's Q-test [27]. Random-effects modelling were used if significant heterogeneity was present ($p < 0.05$) and fixed-effects modelling where heterogeneity was absent. Funnel plots were used to identify publication bias. Sensitivity analysis included removal of studies with a significant delay to surgery in the group not taking clopidogrel (>48 h) and removal of studies that did not control for confounding variables (higher risk of bias). Meta-regression was performed on mortality with the covariates mean age, and gender distribution. All effect estimate calculations were undertaken using Review Manager 5.2 [28]. Meta-regression was performed using Open MetaAnalyst V5.26.14 [29].

Results

Study selection and characteristics

Seventy-five papers were identified with the initial searching of databases (Fig. 1). Nine additional papers were identified after searching of study references and articles that had cited identified studies [24,30–37]. Thirty-one studies deemed to be relevant to the research question underwent full text review. Studies were excluded for the following reasons: Japanese language (1) [35]; paper was unavailable for review (1) [33]; clopidogrel group had a mean time to surgery of >7 days and was therefore felt to be non-comparable (2) [38,39]; letters (3) [36,40,41]; no comparison group (2) [42,43]; no relevant data (1) [34]; abstract only (1) [44]; surveys (3) [22,23,24]; no clopidogrel group (1) [45]; included patients on other antiplatelets (1) [32,46] and early surgery >48 h (2) [47,48] This left 12 studies, which were included in the review [30,31,49–58].

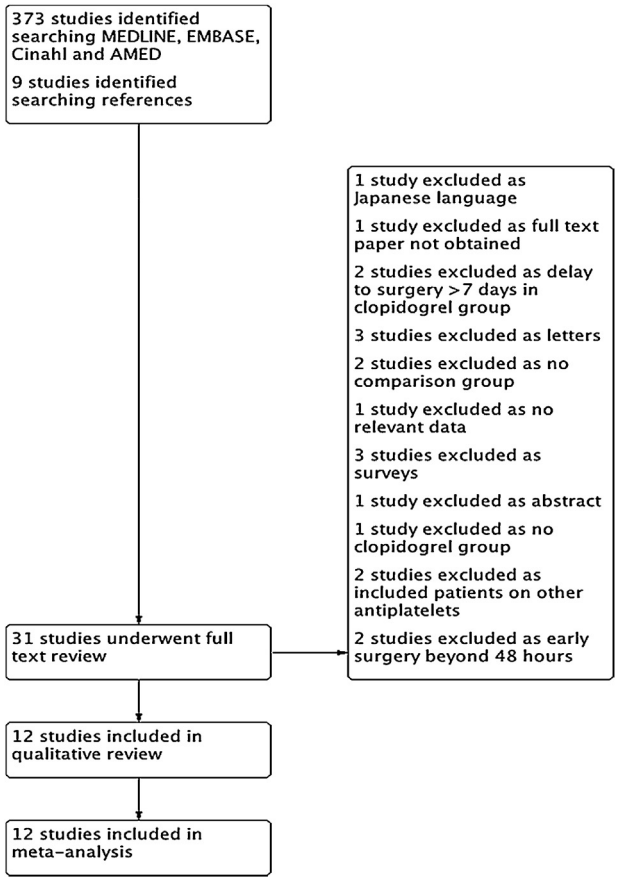

Fig. 1. Flow chart of data acquisition.

No relevant randomised controlled trials were identified; all included studies were observational in design (Table 1). Two comparator groups were used from the studies identified. First, studies comparing early (<2 days) versus delayed surgery (>5 days) in patients admitted on clopidogrel. Second, those with a control group not taking clopidogrel on admission who received early surgery compared with patients taking clopidogrel who underwent early surgery. The mean age of patients was close to that widely reported in the literature for representative hip fracture populations [2,59,60].

Most studies were conducted in Europe, USA or Australia and included both intra and extracapsular fractures. Two studies evaluated intracapsular fractures only. The proportion of patients taking clopidogrel was between 2.5% and 50% where reported. Common exclusions included bleeding disorders, anticoagulants, pathological fractures and polytrauma.

Mortality

Eight studies [30,51–54,56–58] were included in the meta-analysis of mortality at various time points in the clopidogrel versus no clopidogrel group (Table 1). Using the latest reported mortality time point from each of the studies, there was no associated increase in mortality (OR 0.89 (95% CI: 0.58–1.38)) (Fig. 2). There was no evidence of statistical heterogeneity (I^2 = 0%;

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