A survey of the peri-operative management of urological patients on clopidogrel

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ABSTRACT

INTRODUCTION Peri-operative management of patients receiving platelet inhibitors, such as clopidogrel presents a dilemma to surgeons in every surgical specialty including urology. The risk of procedure-related bleeding while continuing clopidogrel needs to be weighed against the risk of thrombo-embolism after discontinuing it. The objective of the survey was to determine current UK practice regarding clopidogrel use/cessation in patients undergoing elective urological procedures.

SUBJECTS AND METHODS A 10-part questionnaire relating to pre- and postoperative clopidogrel use was mailed to all UK urology consultants listed in the British Association of Urological Surgeons' directory.

RESULTS A total of 570 questionnaires were sent and 297 (52%) were returned. The majority of respondents stop clopidogrel prior to TUR surgery (96.6%), major urological surgery (91.7%), TRUS biopsy (90.6%), ESWL (81.8%) and cystoscopy and biopsy (70.1%). The time clopidogrel was stopped pre-operatively and restarted postoperatively was very variable and dependent on local guidelines or urologist preference. Almost half (49.5%) of the respondents would stop clopidogrel irrespective of its indication and 40.7% never consulted a cardiologist/haematologist before stopping clopidogrel. Less than half (43.4%) had a protocol/guideline in place concerning stopping clopidogrel before surgery. Of respondents, 43% do not routinely prescribe bridging therapy after discontinuing clopidogrel. Over half (55%) reported bleeding complications in patients who continued their clopidogrel during urological procedures and 22 (7.4%) of respondents reported an adverse thrombo-embolic event after stopping clopidogrel. The vast majority of respondents (92.8%) felt evidence-based guidelines on clopidogrel use during the peri-operative period would be useful.

CONCLUSIONS This survey has highlighted a significant variation in practice with regards to pre- and postoperative management of clopidogrel in patients undergoing urological procedures. The results of this survey highlight the need for evidence-based guidelines for the peri-operative management of patients on clopidogrel.

KEYWORDS

Clopidogrel – Peri-operative management – Bleeding complications – Thrombosis – Urology – Survey

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Clopidogrel bisulphate (Plavix®) is a thienopyridine derivative which inhibits platelet aggregation and, hence, thrombus formation by irreversibly antagonising the binding of adenosine diphosphate to its platelet receptor.^{1,2} Clopidogrel has been shown to be superior to aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction, or a vascular event in patients with atherosclerotic vascular disease.² Thus, clopidogrel has been recommended as life-long treatment for secondary prevention of ischaemic events following stroke, myocardial infarction, and peripheral vascular disease by the National Institute for Health and Clinical Excellence (NICE).³ Clopidogrel is also indicated following percutaneous coronary stent insertion to decrease the risk of stent thrombosis.⁴ As a result, clopidogrel

alone or in combination with aspirin is increasingly being used to reduce the morbidity and mortality associated with these conditions.⁵

However, clopidogrel can cause excessive bleeding during surgery⁶ as it is an irreversible platelet inhibitor.^{7,8} Simultaneous administration of aspirin and clopidogrel produces additive effects since they both block complementary pathways in the platelet aggregation cascade. While, aspirin irreversibly blocks thromboxane A₂ synthesis by platelets, clopidogrel inhibits ADP-dependent activation of the Gp IIb–IIIa complex causing irreversible inhibition of platelet aggregation.^{1,2,6} The anti-platelet effect of clopidogrel lasts until new platelets are produced. The approximate life-span of a platelet is 8–9 days.⁹ A study in healthy

volunteers showed complete recovery of platelet function 7 days after the last clopidogrel dose.¹⁰ Based on this evidence, the current recommendation is to stop clopidogrel 7 days prior to elective surgery.¹¹ There have been several studies assessing the risk of bleeding in patients on clopidogrel undergoing cardiothoracic surgery,^{7,8} plastic surgery,¹² ophthalmology¹⁵ and vascular surgery.¹⁴ However, conclusions regarding the risk of bleeding are contradictory. To date, there are very few reports in the urological literature regarding the risks associated with clopidogrel and urological surgery. The risk of procedure-related bleeding while taking clopidogrel needs to be weighed against the risk of thrombo-embolism after discontinuation. Inadvertent or premature cessation of clopidogrel prior

to surgical procedures is associated with a higher risk of thrombotic/ischaemic events in this group of patients. This cross-sectional survey was designed to provide a 'snap-shot' of current peri-operative practice in patients on clopidogrel undergoing urological interventions.

Subjects and Methods

A questionnaire (Appendix 1) with a self-addressed return envelope was sent to 570 urology consultants across the UK. Respondents were asked a series of questions relating to their current practice regarding clopidogrel usage in patients undergoing elective surgery (cystoscopy and biopsy, TUR

Table 1 Bleeding complications reported by respondents in patients who continued clopidogrel during urological procedures

Complications	Respondents (n)	As percentage of overall cases
Prolonged/excessive bleeding post-TUR surgery	62	24.0%
Excessive postoperative bleeding	48	18.6%
Excessive bleeding/prolonged haematuria post-TRUS biopsy	13	5.0%
Extensive tissue bruising/large haematoma postoperatively	5	1.9%
Peri-renal haematoma following ESWL	4	1.6%
Severe bleeding after suprapubic catheterisation	4	1.6%
Excessive bleeding post cystectomy/nephrectomy	3	1.2%
Massive haemorrhage following prostatectomy, near death	1	0.4%
Severe haemorrhage post urethrotomy	1	0.4%
Massive pelvic haematoma (Hb 5) post TVT	1	0.4%

surgery and major urological surgery), prostate (TRUS) biopsy and extracorporeal shock wave lithotripsy (ESWL).

Results

A total of 570 questionnaires were posted, with a 52.1% response rate (297 replies). All respondents had encountered patients on clopidogrel in their routine practice. Over half (50.2%) of the respondents encountered more than 5 patients on clopidogrel undergoing urological procedure per month.

Stopping clopidogrel prior to a procedure

The majority of urologists stop clopidogrel prior to TRUS biopsy (90.6%), ESWL (81.8%), TUR surgery (96.6%) and major urological surgery (97.1%). However, this was less frequent in cystoscopy and biopsy (70.1%).

There was considerable variation in the duration of stopping clopidogrel prior to the procedure between different respondents. The majority of respondents stop clopidogrel at intervals between 5 and 14 days before surgery (Fig. 1), with the most frequent interval being 10 days followed by 7 days. A small number of respondents stop the clopidogrel < 3 days or > 14 days prior to the procedure (Fig. 1). Most importantly, a significant proportion (range, 16.3–32.5%) of respondents were unsure or did not have a fixed protocol regarding discontinuation of clopidogrel. Most variation was observed prior to ESWL.

The respondents were then asked whether their decision to stop clopidogrel was based on its indication. Almost half (147 of 297; 49.5%) of the respondents would stop clopidogrel irrespective of its indication. Of these 147 respondents, 105 (71.4%) did not consult a cardiologist/haematologist before stopping clopidogrel.

Of the respondents, 32% ($n = 95$) would routinely consult a cardiologist/haematologist before stopping clopidogrel, 27.3%

($n = 81$) would take their advice occasionally, based on the medical indication for clopidogrel. The remaining 40.7% ($n = 121$) do not consult a cardiologist/haematologist regarding stopping clopidogrel prior to intervention. Three of the respondents specifically stated that they would leave the decision regarding stopping clopidogrel to their anaesthetist.

Bridging therapy

Of respondents, 139 (46.9%) routinely prescribe bridging therapy after stopping clopidogrel, while 29 (9.8%) based their decision on the indication for clopidogrel. The remaining 129 (43.4%) do not use bridging therapy. The commonest agents used for bridging therapy were the low-molecular-weight-heparins (LMWHs; $n = 108$; 64.3%) such as enoxaparin (Clexane®), dalteparin (Fragmin®) and tinzaparin (Innohep®). Thirty-two (19%) respondents would continue aspirin, while 25 (14.9%) would combine a LMWH with aspirin. Three respondents administer heparin after stopping clopidogrel.

Adverse events encountered in patients who stopped clopidogrel

Respondents were asked to report the number and type of thrombotic complications their patients had experienced after stopping clopidogrel. Twenty-two (7.4%) respondents reported an adverse event after stopping clopidogrel. The commonest complication encountered was a cardiac event in 11 patients followed by transient ischaemic event/cerebrovascular accident in 9 and peripheral vascular event in two patients.

Complications encountered in patients who continued their clopidogrel

Thirty-nine (13.3%) of the respondents stated they have never operated on or biopsied a patient who had not stopped clopidogrel for the procedure. Of the remaining 258

respondents, 142 (55%) reported encountering bleeding complications in patients who continued clopidogrel during their surgery/biopsy, the most common of which was prolonged/excessive bleeding post-TURP/TURBT or endoscopic surgery (Table 1). An increased transfusion requirement (range, 4–20 units) and return to theatre after TUR surgery were reported by 24 (9.3%) respondents. Increased bleeding after TRUS biopsy, ESWL, cystectomy, nephrectomy, transvaginal tape (TVT), suprapubic catheterisation and optical urethrotomy were reported (Table 1). The remaining 48 respondents reported excessive postoperative bleeding without specifying the procedure. Three of the respondents specifically

reported an increased operative time due to excessive bleeding/generalised ooze during the surgery.

Restarting clopidogrel after the procedure

The response on the timing of recommencing clopidogrel in the postoperative period is summarised in Figure 2. The variation in practice is clearly evident with a large (range, 9.7–37%) proportion of respondents having no fixed protocol (Fig. 2).

Protocol on the use of clopidogrel during peri-operative period

Less than half of the respondents (43.4%) stated that they had a protocol in place concerning the management of

clopidogrel before surgery or prostate biopsy. The vast majority (92.8%) felt evidence-based guidelines on the use of clopidogrel during the peri-operative period would be useful. Of the remaining ($n = 21$; 7.2%) respondents, some stated that guidelines already existed or that the decision must be made after discussion with cardiologists and individualised to each patient. Two of the respondents considered it a straightforward decision to stop clopidogrel in all cases, and did not think guidelines were necessary.

Discussion

There has been an exponential increase in the use of antiplatelet agents in primary and secondary prevention of cardiovascular, cerebrovascular and peripheral vascular disease. However, data regarding the risks and benefits of continuing or discontinuing therapy with clopidogrel prior to various urological procedures are lacking. Factors that need to be considered in the decision-making process are discussed below.

Indication for clopidogrel

Clopidogrel is used for patients after and for prevention of further cerebrovascular accident, myocardial infarction, acute coronary syndrome, peripheral vascular disease and with coronary stents (bare metal stent, drug eluting stent). Cardiology advice is crucial regarding all patients that have been prescribed clopidogrel but particularly following recent coronary stent insertion.¹⁵ In patients with coronary stents, the main concern of early clopidogrel withdrawal is stent thrombosis, in up to 2% of patients, which most commonly occurs in the first month (sub-acute stent thrombosis). Up to 60% of these patients may have a myocardial infarction and 20–45% of these patients may die after early cessation of clopidogrel.^{4,16} The decision to stop clopidogrel in these patients is dependent on the type of stent used (*e.g.* drug-eluting stent versus bare metal stent), the location of the stent in the coronary vessels (proximal versus distal) and time elapsed since stent insertion.^{4,15,16} Drug-eluting stents have a lower risk of stent stenosis due to an active polymer coating that reduces endothelialisation of the stent and, therefore, have become more popular than bare metal stents.¹⁷ The British Cardiovascular Intervention Society guidelines suggest that clopidogrel can be stopped 1 month after insertion of a bare metal stent and 1 year after insertion of drug-eluting stent (6 months in urgent cases).^{4,16,17} Aspirin should continue in all cases. Non-urgent invasive procedures should be delayed if the risk of bleeding is unacceptable in the presence of clopidogrel. The guidelines state that all minor procedures with a low risk of bleeding can be undertaken without stopping clopidogrel. The guidelines also state that advice should be sought from an interventional cardiologist before stopping clopidogrel in patients with coronary stents.¹⁷ Urology procedures are not mentioned in the guidance.

Duration of stopping clopidogrel and the risk of vascular/thrombotic event whilst off clopidogrel

The Caprie study (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) has shown that clopidogrel is significantly ($P = 0.04$) more effective than aspirin with a relative risk reduction for vascular events of 8.7% in the clopidogrel group.¹ In addition, the Cure study has shown that clopidogrel combined with aspirin reduces mortality, compared with aspirin alone, in patients with unstable angina yielding a 20% relative risk reduction ($P < 0.001$) or an absolute benefit of 2.1%.²

In our survey, a large number of respondents discontinued clopidogrel more than a week prior to the procedure, with some patients waiting up to 2 weeks after cessation of clopidogrel before having their procedure. The impact of discontinuing clopidogrel for prolonged intervals pre-procedure in surgical/urological patients is poorly documented. There have been very few studies looking at risk of a cardiovascular vascular event after cessation of clopidogrel. In patients undergoing non-cardiac surgery the incidence of major cardiac adverse events was found to be significantly higher (13 of 61; 21%) in patients who stopped clopidogrel compared to those who continued clopidogrel peri-operatively.¹⁸ In a survey of patients being admitted to a neurological ward with cerebrovascular accidents, Sibon *et al.*¹⁹ found that 7.3% of patients had clopidogrel stopped prior to their ischaemic stroke. In our survey, 22 respondents (7.4%) reported adverse events in the form of cardiovascular and neurological ischaemic events. Two of our patients presented with thrombo-embolic events (cerebrovascular accident and myocardial infarction) where clopidogrel was stopped greater than 7 days prior to their operative procedure (TURBT and TRUS biopsy).

Risk of procedure-related bleeding when continuing clopidogrel

Several studies have assessed the risk of bleeding in patients on clopidogrel undergoing cardiothoracic surgery^{7,8} and have concluded that performing surgery on patients taking clopidogrel leads to an increased risk of postoperative bleeding, need for transfusion, and a 5–10-fold increased exploration rate.^{7,8,15} A literature search revealed very few studies in the context of urological procedures and concurrent clopidogrel use.^{20–24} In this survey, over half of the urologists report increased bleeding in patients who continued their clopidogrel during procedures. The commonest complication was prolonged/excessive bleeding following transurethral resections, with increased need for transfusion and return to theatre. Severe bleeding after suprapubic catheterisation with need for transfusion was reported by four of the respondents. One of the patients ‘nearly died’ and the other had to be taken to theatre to stop the bleeding after having a suprapubic

Table 2 Our recommendation on cessation of clopidogrel prior to a urological procedures stratified by risk of bleeding

	Risk of bleeding during procedure		
	Low	Moderate	High
Non-urgent procedure	Continue clopidogrel ± aspirin	Delay procedure until clopidogrel can be stopped at recommended time*	Delay procedure until clopidogrel can be stopped at recommended time*
Urgent procedure/ suspicion/treatment of malignancy	Continue clopidogrel ± aspirin	Stop clopidogrel** continue aspirin	Stop clopidogrel** ± aspirin

Based on available evidence and the British Cardiovascular Intervention Society guidelines.⁴

Low bleeding risk procedures include cystoscopy, ureteroscopy ± stone extraction, lasertripsy stone, ureteric stent insertion, laser prostatectomy.

Moderate-risk procedures include inguinoscrotal surgery, bladder or ureteric biopsy, cystohydrodistension, bladder neck incision, TRUS biopsy, transvaginal tape (TVT), SPC insertion, *etc.*

High-risk procedures include TURP, TURBT, major renal, bladder or prostate surgery (open/laparoscopic), PCNL, ESWL, *etc.*

*The British Cardiovascular Intervention Society guidelines.

**After consultation with cardiologist and informed consent from patient.

catheterisation under local anaesthesia. This is particularly significant, as a large number of suprapubic catheter insertions are performed as emergency procedures following retention of urine, where it may not be possible to stop the clopidogrel prior to the procedure. Platelet transfusions along with aprotinin can be given to help reduce significant bleeding. The active circulating metabolite in clopidogrel is excreted in less than 24 h and any exogenous platelets administered after this period are unaffected.²⁵ A recently published double-blind, randomised controlled trial showed aprotinin therapy given intra-operatively decreased postoperative bleeding and the number of transfusions in patients undergoing CABG that had their clopidogrel stopped less than 5 days before surgery.²⁶

Most surgical procedures can be defined as minor, intermediate or major and the expected blood loss can generally be predicted in elective procedures. However, urology may be unique in that a procedure that may be graded as a relatively minor/minimally invasive procedure (*e.g.* TRUS biopsy/ESWL) can pose major difficulties in controlling haemorrhage due to inaccessibility of the organ treated. We, therefore, propose our recommendation based on bleeding-risk categories for urological procedures to aid in the decision process regarding stopping clopidogrel (Table 2).

Type of anaesthesia

The type of anaesthesia is also an important factor when deciding if and when clopidogrel should be stopped. The anaesthetic Royal Colleges recommend stopping clopidogrel a week prior to neuraxial blockade due to the higher risk of spinal haematoma.²⁷

Bridging therapy

In patients with a high risk of thrombo-embolism whilst off clopidogrel, bridging therapy has been used to minimise the risk. However, there are currently no widely accepted guidelines, due to lack of evidence, regarding the use of bridging therapy during temporary discontinuation of antiplatelet agents. The commonest agents used for bridging therapy in our survey were LMWHs. The evidence for use of aspirin as a bridging agent is also lacking although it is recommended as bridging therapy in all patients who have a coronary stent in place.

If clopidogrel is to be stopped, advice must be sought from a cardiologist, if a local guideline is not in place, regarding when it can be safely stopped and what bridging therapy should be used if this is considered necessary.

Restarting clopidogrel

The decision for each patient should be individualised based on the clinical situation (*e.g.* postoperative bleeding, procedure performed, *etc.*). An attempt should be made to restart the clopidogrel as soon as possible after the procedure, when the risk of bleeding is minimal, to minimise risk of thrombo-embolic complications.

Conclusions

This survey has demonstrated a significant variation in practice with regards to the peri-operative management of patients on clopidogrel. A large number of urology units do not have a local policy in place regarding peri-operative use

of clopidogrel. A significant number do not involve a cardiologist in the decision-making process regarding stopping clopidogrel; indeed, a significant number stop clopidogrel regardless of its medical indication. As there are no national guidelines on the management of surgical/urological patients on clopidogrel at present, an approach tailored to the individual patient is required. This approach should be based on the indication for clopidogrel, risks of thromboembolic complications if clopidogrel is discontinued and the risk of procedure related bleeding if clopidogrel is continued. Advice should always be sought from a cardiologist or interventional cardiologist (if coronary stent *in situ*), if no local approved policy or guideline is in place. The patient should be involved in the decision-making process through informed consent highlighting the risk of continuing and discontinuing clopidogrel during the procedure. Stopping clopidogrel without regard for its indication or without advice from a cardiologist, in the absence of a local policy or guideline, exposes the patient to a higher risk of a thrombotic/vascular event and should be avoided at all cost.

Acknowledgement

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Appendix 1: Questionnaire

Dear Colleagues,

Clopidogrel (Plavix) has been increasingly prescribed over the past few years for primary and secondary prevention of vascular ischaemic events in those intolerant of aspirin or if additional therapy is required. A known side-effect is increased risk of bleeding, but there are no wide-spread data available on whether or not it increases operative blood loss, and if or when it should be stopped pre-operatively. For this reason, we are conducting a national survey of current practice with regards to stopping clopidogrel pre-operatively in elective cases. We would be grateful if you could take a few minutes to fill in the questionnaire and return it in the self-addressed envelope.

Thank you for your time,

Regards,

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1. Do you stop clopidogrel before: (if 'unsure or no fixed protocol' please insert '?')

Prostate biopsy	No	Yes	(If yes, how many days pre-operatively?)	_____
Cystoscopy + biopsy	No	Yes	(If yes, how many days pre-operatively?)	_____
TURBT/TURP	No	Yes	(If yes, how many days pre-operatively?)	_____
ESWL	No	Yes	(If yes, how many days pre-operatively?)	_____
Major urological surgery	No	Yes	(If yes, how many days pre-operatively?)	_____

2. Does the reason why the patient is on clopidogrel influence your decision to stop it prior to surgery (e.g. drug eluting coronary stent, cerebrovascular accident, etc.)?

Yes No

3. Do you consult the cardiologist or haematologist before stopping clopidogrel?

Yes No

4. Do you use any other antiplatelet drug/anticoagulant after stopping clopidogrel during the peri-operative period (bridging therapy)?

Yes No

If yes Aspirin Clexane Other (please state) _____

5. Have you encountered any significant morbidity in patients after stopping clopidogrel?

Yes No

If yes, was it Transient ischaemic attack Peripheral vascular event Cardiac event Other (please state) _____

6. If you stop clopidogrel, how soon after the procedure do you advise patients to re-commence it?

Please state (if 'unsure or no fixed protocol' please insert '?')

Prostate biopsy ESWL
Cystoscopy + biopsy TURBT/TURP
Major urological surgery

7. Have you encountered any significant bleeding complications in the peri- or postoperative period in patients who have continued their clopidogrel?

Yes No

If yes, please specify _____

8. Do you have a protocol in place concerning the management of clopidogrel before surgery or prostate biopsy?

Yes No

9. Do you think guidelines detailing when to stop clopidogrel preoperatively would be useful?

Yes No

10. On average, how many patients on clopidogrel do you operate/biopsy in a month?

< 5 5–10 10–15 15–20 > 20

Please feel free to enter any comments in the space below