Perioperative use of methotrexate

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ABSTRACT

Methotrexate (MTX) is the disease modifying antirheumatic 'anchor' drug for the treatment of patients with rheumatoid arthritis (RA). Despite its widespread use and the frequent need of elective orthopaedic and other types of surgical procedures in patients with RA, some confusion exists concerning the use of MTX in the perioperative period. Currently available data do not suggest a need to discontinue MTX because of surgery. There is some evidence that treatment with MTX is safe prior to and after elective surgical procedures. Importantly, disease activity is better controlled when MTX is not interrupted from weekly administration.

Introduction

Patients with various rheumatologic and inflammatory disease states commonly require drugs known to decrease the inflammatory or autoimmune response for adequate control of their condition. Such drugs include non-steroidal antiinflammatory drugs (NSAIDs), cyclooxygenase (COX)-2 inhibitors, corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologic response modifiers. These drugs affect inflammation and local immune responses, which are necessary for proper wound healing in the perioperative setting, thereby potentially resulting in undesirable postoperative complications. Such complications include wound dehiscence, infection, and impaired collagen synthesis. The end result is delayed healing of soft tissue and bone wounds. The current literature provides insight into possible effects of some of these drugs on wound healing.

Methotrexate (MTX) is the most frequently used DMARD for the treatment of chronic inflammatory rheumatic diseases such as rheumatoid arthritis (RA) over the last two decades (1-2). However, there is still confusion about the use of MTX in the perioperative setting of patients with RA. Surgeons often discontinue MTX prior to an elective operation because they fear infectious complications. Any possible impact on the outcome of the surgical procedure from continuation of treatment with MTX has been a matter of debate for many years as well.

Methods

This review on the perioperative use of MTX is based on a systematic literature search using PubMed/medline with the following search terms: Rheumatoid arthritis, methotrexate, postoperative complications, postoperative infections, perioperative complications, corticosteroids.

The review is focused on the following questions:

1. Is continuous MTX therapy in the perioperative setting associated with an elevated risk for complications? Which complications could be attributable to MTX treatment?
2. If MTX should be withdrawn prior to surgery, how long before surgery should this be done? When should the drug be reintroduced after surgery?
3. What is the impact of an elevated disease activity of RA on the surgical outcome?
4. Are corticosteroids in the perioperative setting a better alternative than methotrexate in case of a flare of RA?

Results

Altogether eight papers were identified that address the problem of perioperative complications of patients undergoing DMARD therapy with methotrexate: one review; one paper that addresses solely the complication rate under corticosteroid therapy; and one survey illustrating the confusion among rheumatologists and orthopaedic surgeons about the subject.

None of the identified papers includes data from a randomised controlled study. Three papers report on prospective trials, two of which are randomised

trials and one is an observational study. The remainder of the studies are retrospective trials. Due to the overall rather small patient numbers we decided to present and discuss all of these.

The results of a British survey demonstrate a lot of confusion about the question of perioperative drug management in RA among orthopaedic surgeons and rheumatologists (3). A total of 200 randomly selected orthopaedic surgeons and 200 rheumatologists were asked about their opinion about the use of methotrexate before and after major elective orthopaedic surgery such as joint replacements. Whereas 35% of rheumatologists and 46% of orthopaedic surgeons were concerned that MTX may increase the perioperative risk of complications, only 20% of rheumatologists and 17% of orthopaedic surgeons always stopped MTX prior to elective surgery, and 26% of rheumatologists and 9% of orthopaedic surgeons did so sometimes.

The reasons for discontinuing MTX before surgery varied from blood count abnormalities to drug dose and previous postoperative complications. Interestingly, a wide range of "typical" MTX-dosages was seen among the rheumatologists (37% 2.5–7.5 mg/week, 52% 10–15 mg/week), while only 18% of orthopaedic surgeons knew the exact dosages of MTX for their patients. There was even more confusion about the exact time-point when to stop and when to restart MTX after surgery, varying from 1 to 4 weeks pre- and postoperatively (3).

What evidence is available concerning the questions?

1. In a prospective randomised unblinded trial (4), 388 patients underwent elective orthopaedic surgical procedures including replacement of shoulders, elbows, wrists, hips, knees and ankles, as well as surgery of the metacarpo- and metatarsophalangeal joints. Of those, 88 patients (group A) were treated with MTX in a median dosage of 10mg/week that had started more than 6 weeks prior to surgery and continued medication on a regular basis throughout the perioperative period, while 72 patients (group B) stopped MTX (median dosage 7.5mg/week) 2 weeks before surgery and restarted 2 weeks after the procedure. The remaining patients (group C), which made up the control group, never received MTX. The patients were analysed for wound morbidity such as reddening or discharge of the wound, signs of systemic infection, loosening of implants and other complications requiring revision. While complications occurred in 2 cases of group A (2%, 1 wound dehiscence and 1 discharge from wound), 11 complications (15%) were reported for group B (4 cases with reddening, 4 with discharge from the wound, 1 with dehiscence and 2 other complications). In group C complications were seen in 10.5% of procedures. The groups were further analysed for occurrence of flares in the perioperative period defined as an increase of the Richie-Index >25% and an increase of tender joints >2. RA flares were seen in no patients of group A, in 8% of group B and 4% of group C (p=0.004) 6 weeks after surgery, but no difference in the number of RA flares was seen 6 and 12 months postoperatively. A logistic regression analysis revealed that comorbidities such as diabetes mellitus and concomitant medications were associated with a higher risk of complications, although the study was not powered for this analysis.

In any case, the complication rates were low with no signal of MTX in the lower dose range causing perioperative problems.

2. In another prospective randomised unblinded controlled study (5), 64 patients with planned elective surgery were divided into two subgroups: 32 patients (group A) who underwent 50 surgical procedures discontinued MTX given in a mean dose of 10mg per week 7 days before the procedure, while 32 patients (group B) who had 39 procedures continued MTX on a regular basis. No perioperative infections were seen in any group, and no significant difference was seen in wound healing complications (6 cases of prolonged wound healing in group A, and 4 cases in group B). Differences in RA flares and the influence of other factors potentially contributing to perioperative complications such as comorbidities or concomitant medication were not analysed. However, the results of this study are consistent with the first trial.

3. A recent retrospective 1-year-follow-up study analysed 122 RA patients (6) who had undergone 201 surgical procedures: 48 patients with 77 procedures (group A) continued MTX (average dose 4.3mg/week) regularly perioperatively; 12 patients with 21 procedures (group B) stopped MTX more than 1 week prior to surgery; and the remaining 62 patients with 103 procedures had not been treated with MTX at all. Impaired wound healing occurred in 1.3% of the patients with continuous MTX use, and in 9.5% of the patients with treatment interruption. No difference was seen in the postoperative infection rate between groups, but RA flares occurred more often in the group that had discontinued MTX. Although the mean doses of MTX were rather low, there was clearly no signal in favour of deleterious perioperative effects of MTX.

4. In a small prospective observational study (7), 19 patients underwent 26 elective orthopaedic procedures and continued MTX in a mean dose of 13.1mg/week perioperatively (group A), compared with 13 patients who underwent 16 procedures and discontinued MTX (mean dose 12.5mg/week; group B) two weeks prior to surgery. Whereas 4 postoperative infections were seen in group A (2 infected joint prostheses, one infected joint fusion and one wound infection), no postoperative infection was reported in group B; overall, no RA flares occurred. The authors concluded that temporary discontinuation of MTX prior to joint arthroplasty may decrease the perioperative risk of infection. However, this conclusion may be questioned on the basis of lack of randomisation, small patient numbers, and results of the other studies.

5. In a 10-year retrospective study (8), 60 patients with 91 joint arthroplasties on continuous MTX (group A) were compared to 61 patients (110 joint arthroplasties) who did not receive MTX (group B). A small but not significant difference was seen in the postoperative complication rate between groups (8.7% of procedures in group A *vs.* 5.5% in group B), suggesting that perioperative continuation of MTX does

not have a major impact on the risk of infectious complications.

6. A retrospective study analysed 80 patients (9) who underwent 129 elective surgical procedures on structures of the hand over 5 years. Perioperative complications occurred infrequently, and no significant impact of MTX or corticosteroids on the rates of wound infection or impaired wound healing was seen. Importantly, RA patients with diabetes mellitus (DM) had a strongly increased risk of infection (33% *vs*. 3% without DM).

7. A small retrospective study analysed 38 patients (10) who underwent elective surgery, including 19 procedures in patients who discontinued MTX less than 4 weeks prior to surgery, and 34 in patients who discontinued MTX more than 4 weeks before surgery. While 4 complications (prosthetic joint infection, wound infection or wound dehiscence) were seen in the first group, no complication occurred in the latter group. No clearcut consequences can be derived from this study because of the uncontrolled retrospective design of the study.

8. In another retrospective study, the outcome of 725 surgical procedures in 104 patients undergoing reconstructive ankle and foot surgery for rheumatic deformities was reviewed. The overall complication rate was 32%; no significant correlation of the intake of MTX or corticosteroids with wound healing or infections was observed.

All these cited studies refer to sterile elective orthopaedic surgical procedures – this is appropriate because orthopaedic surgical procedures, although declining in number, are still common in patients with RA (12-14). These procedures usually are elective, and treatment strategies with continuous or discontinued immunosuppressive medication can easily be studied – much better than in emergency cases. Of course, infections are a major threat in immunocompromised patients. An overall infection rate of 3.7% after hip or knee arthroplasty has been reported in RA, and the risk for prosthetic joint infections in patients with RA was increased 4-fold in comparison to patients with osteoarthritis (15).

There is even less data on postoperative complications related to immunosuppressive co-medications in patients undergoing even more difficult procedures such as gut surgery. The perioperative complication rate of patients operated for Crohn's disease was largely unremarkable in terms of association between septic complication rates and the use of high- to moderate-dose steroids, infliximab or immunosuppressives (16). However, only 4 patients had received MTX, 64 patients had azathioprine, and 36 patients had 6-mercaptopurine (16).

Possible evidence for a negative effect of MTX on wound healing is also very limited. Some of the studies shown above not only report on septic complications after surgery but also on wound healing complications, and there is no clear signal for a negative impact of MTX on that. However, one experimental animal study on rats treated with high dosages of MTX given in oncological indications suggests a significant retardation of the early phases of wound fibroplasias (17).

Data on post-operative wound healing in patients with RA receiving corticosteroids are limited as well. In a small retrospective study with a follow-up of 20 months on 100 RA patients undergoing elective orthopaedic surgery that were matched with non-RA patients (18) no difference in the time needed for complete wound healing was found. However, complete wound healing required significantly longer time periods in patients who had taken corticosteroid therapy for more than 3 years (20.3 days) compared to patients with a shorter duration of steroid therapy (15.2 days).

There is no data on the influence of high disease activity of RA on the outcome of elective surgical procedures.

In a recent review it was stated that there is no clear consensus on the issue of immunosuppressive therapy in the context of elective surgical procedures (19).

How can we now answer the questions initially posed?

Although we face a frequent medical problem, only a few studies of acceptable quality have been published on this important topic, some prospective, but many more retrospective. Possible recommendations are based on only 3 studies with more than 100 patients. Analysis of statistical power indicates that 160 patients would be needed in each of 2 groups (total = 320 patients) to show a relative risk of 3 (*e.g*. 15% *vs*. 5%) for postoperative complications in patients treated prior to surgery with MTX, compared to those without (or after discontinuation), at a significance level of 0.05 and power of 0.80 (20). Such a randomised controlled trial has not been performed to date.

One group attempted to conduct a case-controlled prospective multicenter study to address the problem, but failed to enrol 140 patients (21). Unfortunately, the trials published so far have mostly included patients receiving low dosages of MTX. Currently recommended dosages of 15 mg MTX/week initially, with escalation to 20–30 mg/week depending on clinical response and tolerability, have rarely been studied (22). The studied dosages of 5–10 mg/week are too low to address optimally (or adequately) the problem we face in usual clinical practice (23). Nevertheless, we must make the best of what we have.

Overall, the existing data do imply that perioperative use of MTX is not associated with an increased risk of perioperative septic complications, or with an increased risk of impaired wound healing. However, in the absence of data, in individual patients, for example, with a history of previous or severe septic complications, it may reasonable to discontinue MTX therapy and restart after successful wound healing. In that case, the patient should be informed about the possible problem of disease flare and the rheumatologist must monitor the patient closely, together with the orthopaedic surgeon, for timely recognition of changes in the patient's status.

This is important, because the clinician must balance the risks of infection *versus* the risk for a flare of RA which may occur when MTX is discontinued. It is not known whether a flare will have an impact on surgical outcomes. In any case, the patient will not want to experience a flare if avoidable.

The alternative usually is to give (in-

creased doses of) corticosteroids in the perioperative setting. However, corticosteroids may have a negative influence on wound healing and may lead to poor control of glucose levels in people with diabetes, which may also increase perioperative complication rates (4, 9). There is a dose-dependent association between corticosteroid therapy and the risk of serious bacterial infections in patients with RA (24). Use of corticosteroids has also been linked to an increased risk for cardiovascular and cerebrovascular disease (25) – in addition to the often underestimated risk of RA itself for cardiac morbidity (26). Thus, it seems doubtful that the use of corticosteroids will lead to better surgical outcomes than MTX.

For all these reasons, the recommendation nr.9 of the International 3E initiative, that "Methotrexate can be safely continued in the perioperative period in RA patients undergoing elective orthopaedic surgery" (22) is supported by our reading of the literature and our experience with RA patients.

Conclusion

Currently available data do not suggest a need to discontinue MTX because of surgery. There is some evidence that treatment with MTX is safe prior to and after elective surgical procedures. Importantly, disease activity is better controlled when MTX is continuously administered. Interruption of MTX for one week pre-operatively and post-operatively might be a compromise for surgeons and patients who are concerned about complications of surgery induced by MTX. More studies are needed to provide stronger evidence for these statements.

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