

Sequential clot strength analyses following diclofenac in pediatric adenotonsillectomy

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Summary

Background: Tonsillectomy is a common pediatric surgical procedure resulting in significant postoperative pain. There is ongoing controversy as to the most satisfactory analgesic regimen. Nonsteroidal antiinflammatory drugs (NSAIDs) are an alternative to opioids in this setting. NSAID use in tonsillectomy has been shown to be opioid sparing in the recovery period and to have similar analgesic effects to opioids in pediatric patients. Because of their nonspecific action on the enzyme cyclo-oxygenase there is potential for increased bleeding which has led many practitioners to avoid NSAIDs completely in this patient population potentially resulting in suboptimal pain control. Our aim in this study was to assess the effect of preoperatively administered diclofenac on the blood clot strength in children undergoing (adeno-) tonsillectomy.

Methods: Twenty patients undergoing (adeno-) tonsillectomy were recruited into this prospective observational study. All patients received $2 \text{ mg}\cdot\text{kg}^{-1}$ of diclofenac rectally immediately preoperatively. Blood was taken for thromboelastograph analysis pre-diclofenac and 1 and 4 h post-diclofenac administration.

Results: There was a statistically significant increase in maximal clot strength (MA) at 1 and 4 h after diclofenac. Similarly there was a statistically significant reduction in time to initial fibrin formation (R time) post-diclofenac. There was no primary or secondary hemorrhage.

Conclusions: Diclofenac when given preoperatively does not adversely affect clot strength in the immediate postoperative period when the risk of primary hemorrhage is greatest.

Keywords: paediatric; tonsillectomy; NSAID; haemorrhage; thromboelastograph

Introduction

Tonsillectomy is a common surgical procedure in children resulting in significant postoperative pain.

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Opioid analgesia is frequently required, with the unwanted side effects of nausea, vomiting, sedation, pruritus, and respiratory depression (1). Emesis is a frequent tonsillectomy complication and is the most common reason for unanticipated admission following daycase surgery (2). Nonsteroidal antiinflammatory drugs (NSAIDs) are an attractive opioid sparing

agent for pediatric tonsillectomy. They are effective analgesics (3) and have been shown to be particularly useful where tissue inflammation contributes to postoperative pain (4,5). NSAID use in tonsillectomy has been shown to be opioid sparing in the recovery period (5) and to have similar analgesic effects to opioids in children (4,6,7). Because of the nonspecific action of NSAIDs on the enzyme cyclooxygenase (COX1 and COXII), platelet promoting prostaglandins are inhibited resulting in decreased platelet aggregation and potentially increased bleeding. The use of these agents has thus been somewhat limited by reports of increased postoperative bleeding, particularly with ketorolac. Prospective randomized studies have shown that preoperatively administered intravenous ketorolac increased perioperative blood loss and increased posttonsillectomy bleeding without any beneficial effects (8,9). Other NSAIDs have been similarly implicated, however, these studies have been contradictory. Some authors have reported increased intraoperative blood loss (10), increased reoperation (11) and increased secondary hemorrhage (12). The NSAID, diclofenac, which has much greater COXII selectivity than ketorolac, has not been shown to increase peri- or postoperative blood loss whether given pre- or postoperatively (13–16). Similar results have been found for other NSAIDs (6,17,18).

The policy in our unit is to use a multimodal approach to analgesia for tonsillectomy comprising paracetamol and the NSAID diclofenac, with addition of an opioid if required. We administer $40 \text{ mg}\cdot\text{kg}^{-1}$ of paracetamol with $2 \text{ mg}\cdot\text{kg}^{-1}$ of diclofenac as lower doses of both have been shown to be ineffective (10). The combination of an NSAID plus paracetamol reduces the need for supplementary analgesia by 50% in pediatric tonsillectomy patients (17). Studies have suggested that analgesia is frequently inadequate in children undergoing tonsillectomy (10,19). As many clinicians wish to avoid opioid related side effects in this setting, particularly in obstructive sleep apnea and daycare tonsillectomy, it may be that children receive second class pain management because of a perceived risk of nonsteroidal agents rather than a fully substantiated one.

We therefore aimed in this study to assess the effect of the NSAID diclofenac, administered preoperatively, on the viscoelastic properties of

blood clotting as assessed by thromboelastography (TEG).

Methods

This was a prospective, observational study. 20 ASA grade I–II patients aged 2–15 years were recruited into the study. Patients were scheduled to undergo elective tonsillectomy or adenotonsillectomy and were sequentially recruited. Institutional ethics committee approval was obtained. Informed parental consent was gained for each patient. We excluded patients with a known history of bleeding diathesis, hypersensitivity to NSAIDs or poorly controlled asthma. A history of aspirin use in the previous 5 days or NSAID use in the previous 48 h also precluded entry into the study. Following induction of anesthesia all patients received $2 \text{ mg}\cdot\text{kg}^{-1}$ of diclofenac and paracetamol $40 \text{ mg}\cdot\text{kg}^{-1}$ both administered rectally. Further analgesia was at the individual anesthetist's discretion. Surgery was carried out by one consultant surgeon using a dissection technique with bipolar forceps. Adenoidectomy was performed by curettage.

Each patient had blood samples taken at three distinct points in time: Time 0 – immediately preadministration of diclofenac; Time 60 – 1 h postadministration of diclofenac; and Time 240 – 4 h postadministration. Blood was taken from an i.v. cannula using a two syringe technique. The initial 2.5 ml was discarded to avoid contamination from tissue thromboplastin. A 1 ml sample of whole blood was then taken and added to a test tube containing kaolin within 4 min; 360 μl of this sample was transferred to a heated cuvette and underwent TEG analysis at 37°C . (Hemoscope Corporation, Skokie, IL, USA).

The TEG analyser was calibrated and warmed to 37°C . For each of the 20 participating patients the following TEG parameters were measured at Time 0, Time 60 and Time 240 respectively; R Time (time to initial fibrin formation), K Time (measure of the speed of clot strengthening), alpha angle (speed of clot formation) and maximum amplitude (MA). MA, measured in mm, is the greatest amplitude on the TEG trace. It is a reflection of the absolute strength of the fibrin clot and is a direct function of the maximum dynamic properties of fibrin and platelets (20) (Figure 1). Results are recorded as

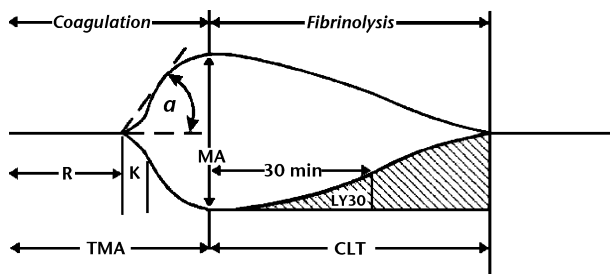


Figure 1
Diagram of normal thromboelastogram. Reaction time (R time) (sec), time to initial fibrin formation; K time (sec) speed of clot strengthening – time from R to the point where the amplitude on the tracing reaches 20 mm; alpha angle (deg) speed of clot formation; maximum amplitude (mm) measures absolute clot strength; LY30, percent clot lysis 30 min after MA.

median \pm interquartile range. Shapiro Wilk analysis was used to test for parametricity of data. We used the Friedman test for nonparametric repeat measures to compare the changes in R time, K time, α -angle, and MA for each patient. Intergroup comparisons were performed using Tukey analysis. Significance was tested at the 5% level.

Results

Of the 20 patients recruited, eighteen patients had blood sampled at Time 0, Time 60, and Time 240. Two patients did not have blood samples taken at the third time point (Time 240) because of malfunction of the i.v. cannula. None of the 20 patients had significant perioperative bleeding and there were no cases of secondary hemorrhage. In total, 232 TEG measurements were recorded.

The Friedman test demonstrated a significant reduction in R time ($P = 0.008$) and a significant increase in MA ($P < 0.001$) (Table 1). Tukey analysis

Table 1
TEG parameters at the three study time points. Results presented as median \pm interquartile range

	Time 0	Time 60	Time 240
R time (s) ^a	5.6 (4.47–7.62)	4.6 (4.0–5.4)	3.95 (3.0–5.2) ^c
K time (s)	1.7 (1.45–2.0)	1.35 (1.17–1.75)	1.4 (1.12–1.72)
Alpha angle (degrees)	66.6 (62.4–69.7)	69.7 (66.0–73.9)	69.2 (66.0–72.6)
MA (mm) ^b	68.8 (66.0–72.1)	71.0 (68.7–72.9) ^c	71.0 (68.3–72.8) ^c

All results median (\pm IQR).

^a $P = 0.008$; ^b $P < 0.001$.

^c $P < 0.05$ vs Time.

demonstrated a significant reduction in R time between Time 0 and Time 24, and significant increases in MA between Time 0, and both Time 60 and Time 240 (Figure 2).

Discussion

In this study rectal diclofenac administered preoperatively at a dose of $2 \text{ mg}\cdot\text{kg}^{-1}$ did not reduce clot elastic strength as assessed by TEG. We found a statistically significant increase in MA measured at 1 and 4 h post-diclofenac administration compared with baseline (pre-diclofenac administration), and a significant reduction in R time. This would indicate that the patient was in a hypercoagulable state at the points of measurement compared with baseline, which may have been a result of the surgery itself (21). The measurements however were still within the normal range for this patient population (25).

We used TEG to assess the response of the coagulation system to diclofenac, rather than traditional coagulation tests which are based on static isolated endpoints of standard laboratory tests and do not take into account the interaction of platelets with the clotting cascade in whole blood. TEG, in contrast, measures this interactive dynamic coagulation process, providing a complete evaluation of the process of clot initiation and the structural characteristics of the formed clot and its stability. The “signature” of generated tracings gives information on clotting factor activity, platelet function and any clinically significant fibrinolytic process within 20 min (20). Thromboelastography has been validated in liver transplant surgery (22), cardiac surgery (23), and obstetrics (24), where its use has led to improved detection and treatment of coagulopathy resulting in decreased transfusion of blood products. Normal values have also been described for children (25).

The putative antiplatelet effects of diclofenac should be reflected in the TEG maximum amplitude. Platelet abnormalities whether quantitative or qualitative significantly disturb the MA (26,27). Previous studies with aspirin have failed to show an effect on TEG despite aspirin’s well described anti platelet effects (28). However, all these studies used low-dose aspirin which may not have sufficiently disrupted platelet function to alter TEG parameters.

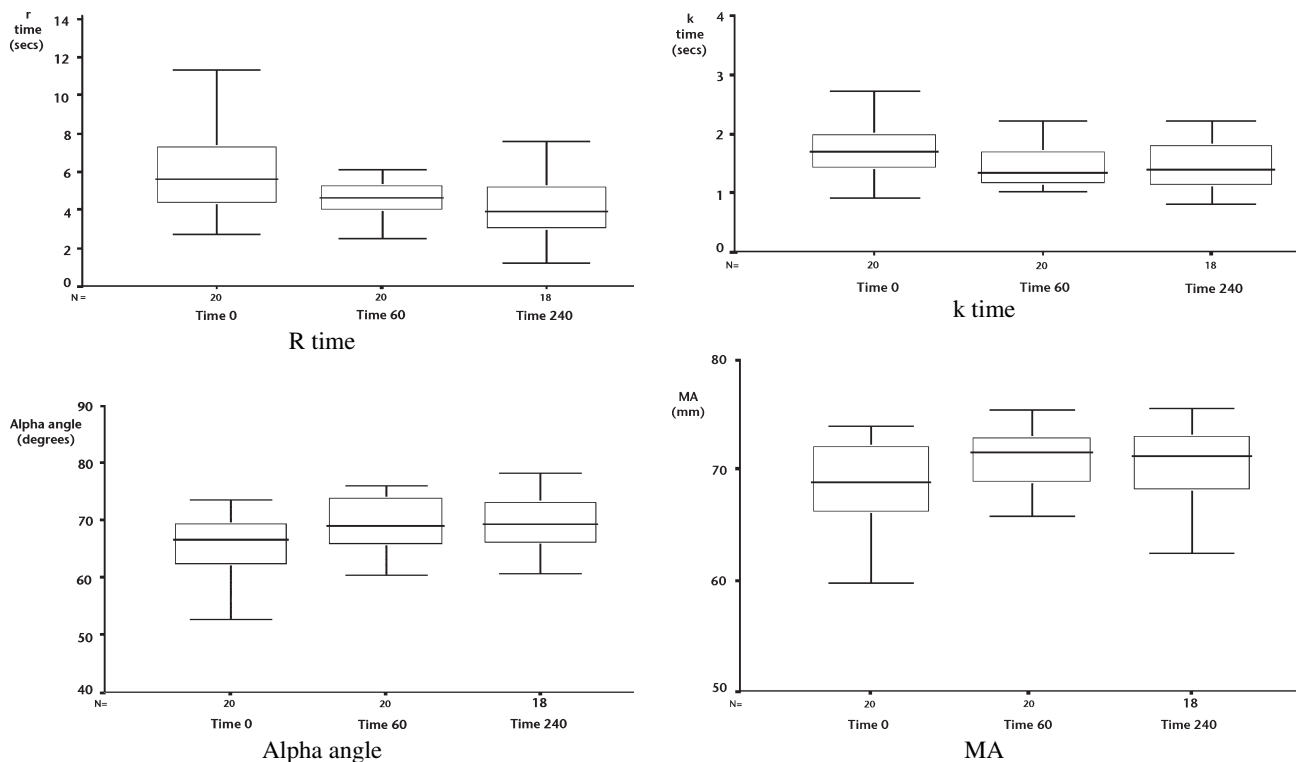


Figure 2 Box and whisker plots of TEG variables at three time points.

We used a higher dose of rectal diclofenac ($2 \text{ mg}\cdot\text{kg}^{-1}$) compared with previous studies (4,10) and this would be expected to result in plasma drug levels sufficient to decrease platelet aggregation, which in turn would have been apparent on the thromboelastograph. The selected time points should have captured peak plasma concentrations which have been shown to occur at 50 min in this population (29).

Alternatively conventional TEG may not in fact have been the most appropriate tool to assess the antiplatelet effects of diclofenac, as platelet inhibition may have been masked by the much greater contribution of thrombin to clot formation. A recently developed tool – modified thromboelastography (mTEG) which can generate clot in the absence of thrombin, thus isolating the platelet contribution to clot formation has been shown to be affected by aspirin therapy (30). Whether diclofenac would have similar effects on mTEG has not been studied.

Patients who do not receive NSAIDs may have an even greater procoagulant response to surgery and diclofenac may merely have attenuated this. The changes in thromboelastograph measurements that we observed, while statistically significant may not indicate clinical hypercoagulability as has previously been shown in pediatric cancer patients (31).

A potential weakness with our study was the absence of a control group. It is standard practice in our hospital that all patients undergoing tonsillectomy receive NSAIDs unless contraindicated, so we did not recruit patients who did not receive NSAIDs at any part of their perioperative course. The time frame of the study may also be a limiting factor as we only examined the first 4 h postsurgery, but this is when the risk of primary hemorrhage is greatest and peak plasma levels of diclofenac would have been captured during this period.

Whether repeat dosing NSAID would result in similar effects on coagulation and TEG measurements warrants further investigation.

Diclofenac administered preoperatively at a dose of 2 mg·kg⁻¹ did not adversely affect clot elastic strength in children undergoing adenotonsillectomy.

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