Kliiniline küsimus nr 6

Kas patsiendil **peri**operatiivne NSAIDide manustamine vs mittemanustamine mõjutab perioperatiivse veritsuse tekke tõenäosust?

Kriitilised tulemusnäitajad: kordusoperatsioon veritsuse tõttu, operatsiooni aegne verekadu, postoperatiivne verekadu, valuvaigistitest (opiaadid) tingitud kõrvaltoimed, rehospitaliseerimine veritsuse tõttu, postoperatiivsete tüsistuste esinemissagedus

Background

In the perioperative period, one of the main concerns regarding the use of conventional NSAIDs is that they interfere with platelet function and might thus increase the risk of reoperation for bleeding and increase surgical blood loss. COX-2 inhibitors do not affect platelet function.

Available conventional NSAIDs and COX-2 inhibitors on the Estonian market (as of 29.05.2014)

Toimeaine, periop perioodi sobilik ravimvorm	Näidustus SPCs	C max	T 1/2
Diklofenak (enterotabl 50m suposiit, süstelahus)	Valu ja põletiku sümptomaatiline ravi	Enterotablett: kesmiselt 2-3 (1-16h) Rektaalselt: 30min	1-2h (aktiivsetel metaboliitidel 1 - 3 h)
Ibuprofeen (tabl. 200m 400mg, 600mg) - võimal ainult pre- ja posto manustamine	Nõrk kuni mõõdukas valu	1-2h	Umbes 2h
Ketoprofeen (tabl 25m 50mg, 100mg, süstelahus)	Valu	Tabl: 1h	2-3h
Deksketoprofeen (12,5mg 25mg tabl; süstelahus)	Nõrga kuni mõõduka valu sümptomaatilir ravi Süstelahus: Mõõduka kuni tugeva va sümptomaatiline ravi, sh. postoperatiivr valu	Tabl: umbes 3 min (15-60min)	Tabl: 1,65h
Etorikoksiib (tabletid 30m 60mg, 90mg ja 120mg) võimalik ainult pre- ja posto manustamine	Osteoartroosi, reumatoidartriic anküloseeriva spondüliidi ning ägec podagrahooga seotud valu põletikunähtude sümptomaatiline rav Kirurgilise hambaraviga seotud mõõduk valu lühiajaline ravi.	1h	22h
Tselekoksiib (kapslid 100m 200mg) - võimalik ainult pre- postop. manustamine	Osteoartroosi, reumatoidartriidi anküoseeriva spondüliidi sümptomaatilir ravi täiskasvanutel	2-3h	8-12h

Treatment guidelines

1. **Guideline DE-07** gives specific reccommendations for perioperative use of NSAIDs for different types of surgeries based on the perioperative bleeding risk.

For **tonsillectomy** this guideline refers to 4 metaanalysis that assessed the bleeding risk related to the preoprative NSAID administration and none of them concluded that the bleeding risk is significantly increased (**LoE: 1a**) (Krishna et al., 2003; Marret et al., 2003; Moiniche et al., 2003; Cardwell et al., 2005) (table 1).

Total hip arthroplasty: perioperative NSAID administration is associated with increased risk of intra- and postoperative bleeding risk (based on 3 RCT). (table 2)

Total knee arthroplasty: bleeding risk was not increased with perioperative NSAIDs use (table 3)

Craniotomy: Due to the bleeding risk, NSAIDs should not be used postoperatively. Bleeding risk after craniotomy associated with NSAID use. (LoE: 4) (Palmer *et al*., 1994).

2. **Guideline AU-10** stated that perioperative non-selective NSAIDs increase the risk of severe bleeding after variety of operation compared with placebo and need for reoperation due to bleeding after tonsillectomy, but coxibs do not impair platelet function thus reduce the risk of perioperative blood loss in comparison with non-selective

Tonsillectomy: Non-selective NSAIDs do not significantly increase blood loss after tonsillectomy but do increase the need for reoperation due to bleeding (N) (Level I).

Perioperative non-selective NSAIDs increase the risk of severe bleeding after a variety of other operations compared with placebo (N) (Level II).

Coxibs do not impair platelet function; this leads to reduced perioperative blood loss in comparison with non-selective NSAIDs (S) (Level II)

1.“Behandlung acuter perioperativer und postraumatischer Schmertzen” 2009 (DE-07)

The grading system of the guideline

Degree of recommendation	Level of evidence	
A	**1a**	Systematic review of controlled randomized clinical trials
	1b	Controlled randomized clinical trials with a strict confidence interval
	1c	“All or nothing” therapeutic results
B	**2a**	Systematic review of cohort studies
	2b	Cohort studies (including lesser quality randomized clinical trials)
	2c	Observation of therapeutic results (outcomes research).
	3a	Systematic review of case-control studies
	3b	Case-control study
C	**4**	Case report (including cohort or case-control of poor quality)
	5	Specialists’ opinions lacking critical evaluation or based on basic matters (physiological study or study with animals)

Original tables (translated) from the guideline:

Table 1. Tonsillectomy: NSAID vs. alternative

	Author, year; Evidence level	**Studies**	**Therapy**	**Result**
1	Cardwell *et al*., 2005; LoE: 1a	13 RCTs Metaanalyse	NSAID pre-intra-postop	Bleeding risk ↔ Risk of reoperation ↔
2	Moiniche *et al*. 2003; LoE: 1a	25 RCTs	NSAID pre-postop.	Bleeding risk ↔ Risk of reoperation after postop. administration ↑; bei preop. administration ↔
3	Krishna *et al*. 2003; LoE: 1a	5 RCTs, Metaanalyse	NSAR postop.	Bleeding risk ↔
4	Marret *et al*. 2003; LoE: 1a	7 RCTs, Metaanalyse (Only 2 studies included adults, n= 77, administered im ketorolac, iv ketoprofen)	NSAID postop.	Bleeding risk ↔ Risk of reoperation ↑

1. **Cardwell *et al*.**

Primary objective: to assess the effects of NSAIDs on bleeding with paediatric tonsillectomy.

Results: NSAIDs did not significantly alter the number of perioperative bleeding events requiring surgical intervention: Peto odds ratio (OR) 1.32 (95% confidence interval (CI) 0.47 to 3.70).

Eight trials involving 532 children looked at bleeding not requiring surgical intervention. NSAIDs did not significantly alter the number of perioperative bleeding events not requiring surgical intervention: Peto OR 1.00 (95% CI 0.39 to 2.53).

Conclusion: NSAIDs did not cause any increase in bleeding that required a return to theatre.

2. **Møiniche *et al.***

Primary objective: incidence of perioperative bleeding at tributable to the use of NSAIDs in patients undergoing tonsillectomy

Results: 9 studies were in adults, 14 in children and 2 in both adults and children.

In 9 studies with 12 treatment arms, a NSAID was administered before tonsillectomy, and intraoperative blood loss was an end point.

Mean measured blood loss was 2.1+/- 0.9 mL/kg with a NSAID compared with 1.8 +/- 0.9 mL/kg with the control. The WMD (weighted mean difference) was not significantly different (WMD, 0.38 mL/kg; 95% CI, 0.06 to –0.81).

With NSAIDs, 10.7% patients had postoperative bleeding compared with 9.4% control patients, a difference that was not statistically significant and independent of the model used.

Readmission or unanticipated admission because of bleeding was reported in 8 studies with 9 treatment arms. With NSAIDs, the range of admissions was 0% to 15%, and with controls, the range was between 0% and 10%.

Conclusion: the evidence for NSAIDs to increase the incidence of bleeding after tonsillectomy remains ambiguous.

3. **Krishna *et al.***

Objective: to determine the risk of postoperative hemorrhage associated with the use of NSAIDs after tonsillectomy.

Results: For the 1368 patients included in analysis, the pooled OR of posttonsillectomy hemorrhage with NSAIDs compared with controls was 1.29 and was not statistically significant (95% CI, 0.85-1.73; $P \geq .05$). A subgroup analysis revealed an odds ratio of 0.93 (95% CI, 0.44 -1.95; $P \geq .05$) for the nonaspirin NSAID group,

Conclusion: There appears to be no significant increased risk of bleeding for nonaspirin NSAIDs in this meta-analysis.

4. **Marret *et al*.**

Objective: to evaluate the risk of bleeding after tonsillectomy in patients treated postoperatively with NSAIDs

Results: Of the 243 patients who did not receive NSAID therapy, 13 had primary or secondary postoperative bleeding (5.3%; range, 0–25%) (fig. 2). In 7 of these 13 controls, the bleeding was secondary. Of the 262 patients who received NSAID therapy postoperatively, 24 (9.2%; range, 0–25%) had postoperative bleeding (odds ratio, 1.8; 95% CI, 0.9–3.4). The bleeding was primary for nine patients in the NSAID group.

Of the 262 patients given NSAID therapy postoperatively, 11 required reoperation for hemostasis. The bleeding was primary in five patients and secondary in six patients (four children and two adults). Two control patients required reoperation for hemostasis. The bleeding was primary in one patient and secondary in one patient. These figures translate into a significant difference in the rate of reoperation for hemostasis, with 0.8% for the

controls and 4.2% for the NSAID-treated patients (odds ratio, 3.8; 95% CI, 1.3–11.5;*P* = 0.02) (fig. 3). This indicates a 425% increase in the odds ratio. The number needed to harm was 29 (95% CI, 17–144).
Conclusion: postoperative use of conventional NSAIDs such as ketorolac, ibuprofen, or ketoprofen increases the risk of reoperation for hemostasis after tonsillectomy. These drugs should not be used after tonsillectomy.

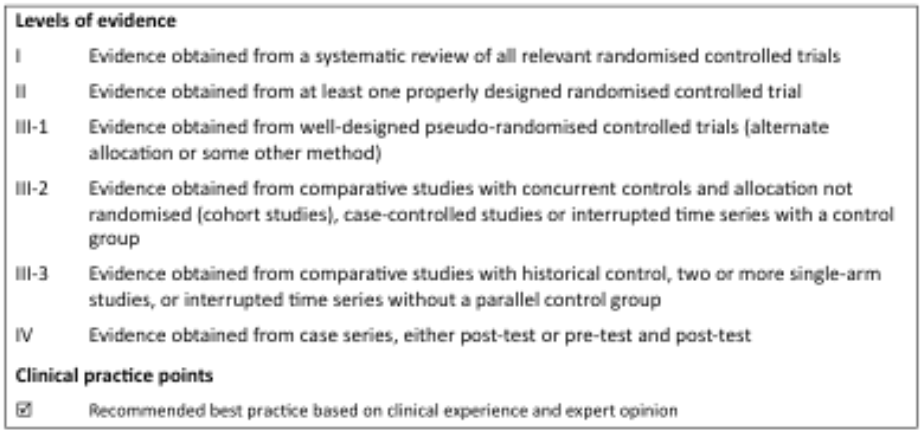
Table 2 Total hip arthroplasty: perioperative NSAID vs. placebo/no intervention

Author, year, Level of evidencel	Patients	Therapy	Results
Bugter *et al*., 2003; LoE: 1b	n= 50	Ibuprofen preop.	intra-and postoperative bloodloss ↑
Slappendel *et al*., 2002; LoE: 1b	n= 50	Ibuprofen preop	intra-and postoperative bloodloss ↑
Alexander *et al*., 2002; LoE: 1b	n= 102	1. Diclofenac i.v. preop 2. Ketorolac i.v. preop.	Bleeding / reoperation risk not reported
Fletcher *et al.,* 1995; LoE: 1b	n= 60	Keterolac preop.	Bleeding / reoperation risk not reported
An *et al*., 1991; LoE: 1b	n= 140	NSAID preop.	intra-and postoperative bloodloss ↑

Table 3 Total knee arthroplasty: postoperative NSAID vs. Placebo (only these studies are included here where bleeding risk is reported)

Author, year, level of evidence	Patients	Therapy	Result
Dahl *et al*. 1995; LoE: 1b	n= 123	1. Ibuprofen 2. Ibuprofen + Codein postop.	Blood loss ↔
Laitinen und Nuutinen, 1992; LoE: 1b	n= 40	Diclofenac postop.	Blood loss ↔
Segstro *et al*., 1991; LoE: 1b	n= 50	Indomethacin postop.	Blood loss ↔
Buvanendran *et al*., 2003; LoE: 1b	n= 70	Rofecoxib pre- und postop.	Blood loss ↔

2. Acute Pain Management: Scientific Evidence 2010 (AU10)



Levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-controlled studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test and post-test

Clinical practice points

☑ Recommended best practice based on clinical experience and expert opinion

Guideline reffers to **2 meta-analyses of tonsillectomy** in both adult and paediatric patients (Marret *et al.* 2003 Level I; Moiniche *et al.* 2003, Level I) where non-selective NSAIDs were found to increase the risk of reoperation for bleeding (number needed to harm (NNH) 29 to 60), but surgical blood loss was not significantly increased (Moiniche *et al*. 2003, Level I).

Guideline also refers to 4 studies:

After a variety of different operations, the use of non-selective NSAIDs showed a significant increase in risk of severe bleeding from 0 to 1,7% compared with placebo (NNH 59) (Elia et al. 2005, Level I). **Bleeding risk ↑**

This was also found after **hip replacement** where ibuprofen group (452 to ibuprofen and 450 to placebo) had significantly increased risk of major bleeding complications (OR 2,1). There were no significant differences between groups in the proportion of patients requiring red cell transfusion (ibuprofen 37% v placebo 34%, P=0.35), suction drainage volumes (415 ml v 424 ml, P = 0.71), or postoperative haemoglobin concentrations measured ≥ 48 h after surgery (105 g/l v 105 g/l, P=0.80) (RCT by Fransen et al 2006, Level II). **Bleeding risk ↑**

After **gynaecological breast surgery**, use of diclofenac led to more blood loss than rofecoxib. There was an increased estimated blood loss (all patients (n=50), standardized effect size 1.22 SD, 95% CI 0.65±1.78 SD, P<0.01; subgroup (n=38), standardized effect size 0.87 SD, 95% CI 0.20±1.53 SD, P=0.01), and a greater reduction in haemoglobin in the diclofenac compared with the rofecoxib group (all patients (n=50), mean difference ±4 g litre±1, 95% CI ±7 to ±1, P<0.01; subgroup (n=38), mean difference ±4 g litre±1, 95% CI ±7 to ±1, P=0.01). (single-centre, double-blinded, active controlled study by Hegi et al. 2004 Level II).

After **othorinolaryngological surgery** in an outpatient setting, tenoxicam increased bleeding at the surgical site. Surgical site bleeding occurred in 18 of 171 (10.5%) patients on tenoxicam and one of 57 (1.8%) on placebo (P=0.026); of these, nine in the tenoxicam group and 0 in the placebo were classified as major (P=0.07). (prospective, controlled, double-blind, multi-centre study Merry *et al.* 2004, Level II). **Bleeding risk ↑**

Type of the surgery, perioperative NSAID administration and perioperative bleeding risk (Guideline DE-07 and PROSPECT reccomendations)

Type of the surgery	DE-07		PROSPECT	
	Conventional NSAID	**COX-2 inhibitor**	**Conventional NSAID**	**COX-2 inhibitor**
Head surgery	**POSTOP**: not recommended- **Bleeding risk ↑** (LoE: 4)	-	-	-
Tonsillectomy	Paracetamol should be preferred GoR: B	Not recommended GoR: B		
Total hip arthroplasty	**PREOP:** not recommended GoR:A **POSTOP** reccommended GoR: A	-	**PREOP:** not recommended (grade A) **Bleeding risk ↑** **POSTOP**: reccommended (Garde A)	Should be administered in enough time to provide sufficient analgesia when the patient wakes (grade D); this could be pre-operatively since there is no increased risk of periop blood loss (Grade B) **Bleeding risk ↑**
Total knee arthroplasty	**POSTOP:** reccommended GoR: A		**PREOP:** not recommended (Grade B) **Bleeding risk ↑** (LoE 1) **POSTOP**: reccommended (Garde A)	**POSTOP**: reccommended (Garde A) Should be administered at the appropriate time to provide sufficient analgesia in the early recovery period (Grade D, LoE 4) **POSTOP**: reccommended (Garde A)

Laparoscopic cholecystectomy	-	-	**PREOP**: not reccomme (LoE1) **INTRAOP**: recommend end of surgery to ensu analgesia when the pat wakes up (Grade D), provided haemostasis i (LoE 4) **POSTOP**: recommende	**PREOP:** recommended (Gr **INTRAOP**: recommended a end of surgery to ensure analgesia when the patient wakes up (Grade D), provided haemostasis is se (LoE 4) **POSTOP**: reccommended (
Thoracotomy	-		**PRE- and INTRAOP:** not recommended - risk of bleeding (Grade B) **POSTOP**: recommended (grade A) Not recommended in patients with increased bleeding risk (Grade B)	**PRE- and INTRAOP:** not recommended (Grade D) **POSTOP**: recommended (Grade B)
Abdominal hysterectomy	-		**PREOP:** not recommended- (grade A). **Bleeding risk** ↑(grade A) **POSTOP**: recommended (Grade A) Not recommended in patients with increased bleeding risk (Grade B)	**PREOP:** recommended (Grade A)
Colonic resection	-	-	**PREOP**: not recommended (Grade B) **Bleeding risk** ↑ (LoE 1) **POSTOP**: recommended (Grade A), Not recommended in patients with increased bleeding risk (Grade B, LoE 1)	**PRE- and INTRAOP:** recommended (Grade B, LoE 2), only for patients who do not receive epidural analgesia (LoE 4) **POSTOP**: recommended (Grade B) COX-2-selective inhibitors may be preferred to conventional NSAIDs in the peri-operative setting, in patients who have an increased risk of bleeding (transferable, LoE 1)
Hemorrhoid surgery	-	-	**PREOP:** should be administered at the appropriate time to provide sufficient analgesia in the early recovery period (Grade B, LoE 1) **POSTOP**: recommended (Grade B, LoE 1)	**PREOP:** should be administered at the appropriate time to provide sufficient analgesia in the early recovery period (Grade B, LoE 1) **POSTOP**: recommended (Grade B, LoE 1)
Herniorraphy	-	-	**PRE- and POSTOP:** recommended **(Grade A)** Not recommended in patients with increased bleeding risk (Grade B)	**PRE- and POSTOP:** recommended (Grade A) COX-2-selective inhibitors may be preferred to conventional NSAIDs in the peri-operative setting, in patients who have an increased risk of bleeding (Grade B)

Non-cosmetic breast surgery	**PREOP:** not reccommended (Grade B), **Bleeding risk** ↑ *vs.* control (LoE 1) and *vs.* COX-2-selective inhibitors (LoE 1) **POSTOP**: recommended (Grade A)	**PREOP:** in short breast surgery procedures is recommended (Grade D, LoE 4), for prolonged surgery not recommended (Grade D, LoE 4) **POSTOP**: recommended (Grade B)
Radical prostatectomy	**INTRA and POSTOP:** not recommended (GoR B)	All analgesics should be administered at the appropriate time (pre- or intra-operatively) to provide sufficient analgesia in the early recovery period (GoR D) **POSTOP**: recommended (GoR B)

Süstemaatilised ülevaated

Kokkuvõte süstemaatilistest ülevaadetest

Two of the 2 meta-analyses found that the bleeding risk is increased by the perioperative use of conventional NSAIDs.

Kokkuvõte (abstract või kokkuvõtlikum info)

1. Riggin *et al*. 2013 Bleeding risk ↔

Objective: To compare bleeding rates and severity between recipients of NSAIDs versus placebo or opioid analgesics for tonsillectomy.

36 studies included to the meta-analysis 1446 adults and 1747 children
When all of the studies were combined using the most severe outcome, there was no increased risk of bleeding in those using NSAIDs after **tonsillectomy**.
Use of NSAIDs in general [1.30 (0.90–1.88)] was not associated with increased risk of bleeding, most severe bleeding, secondary haemorrhage, readmission or need of reoperation due to bleeding. Similarly, there was no increased bleeding risk for specific NSAIDs in adults. In 15 studies NSAID administered **peri**operatively and to adults. These studies show various results.
Use of NSAIDs in children [1.06 (0.65– 1.74)] was not associated with increased risk of bleeding in general, most severe bleeding, secondary haemorrhage, readmission or need of reoperation due to bleeding. Similarly, there was no increased bleeding risk for specific NSAIDs in adults. In the studies looking at paediatric subjects, the overall odds ratio of bleeding was even lower than in the general population and not significant. This result is based on 18 studies, six of which had zero outcomes in either treatment arm.
C**onclusion**: These results suggest that NSAIDs can be considered as a safe method of analgesia among children undergoing tonsillectomy.

2. Maund *et al*. 2011 Bleeding risk ↑

Objective: The aim of our study was to apply the technique of MTC analysis to determine explicitly which class, if any, of non- opioid analgesic (paracetamol, NSAIDs, or COX-2 inhibitor) is most effective at reducing morphine consumption and morphine-related adverse effects when used as part of multimodal analgesia after **major surgery.**

60 trials included: paracetamol or propacetamol (n=12), COX-2 inhibitors (n=16), and 38 were of NSAIDs (n=38). 6 studies comparing NSAID with placebo reported the primary non-opioid outcome of interest, surgical bleeding. Overall, 2.4% of participants receiving an NSAID experienced surgical- related bleeding compared with 0.4% receiving placebo.

2. Elia *et al.* 2005 Bleeding risk ↑

Aim: to quantify and to compare the morphine-sparing capacity of acetaminophen, NSAIDs, and COX-2 inhibitors after major surgery and to test the evidence that their use in conjunction with morphine PCA provides a clinically relevant benefit.

52 RCTs were included in this meta-analyse (4,893 adults) testing acetaminophen, NSAIDs (ketorolac, diclofenac, ketoprofen) or COX-2 inhibitors given in conjunction with morphine after surgery.
Patients underwent **major orthopedic** (13 trials), **abdominal** (12), **gynecologic** (16), **spine** (9), or **thoracic** (2) procedures.
33 trials (1,509 patients) tested different NSAIDs as single- dose regimens, multiple-dose regimens, or continuous infusions. 14 (1,019 patients) tested COX-2 inhibitors as single-dose or multiple-dose regimens.
9 NSAID studies reported on presence or absence of surgical bleeding complications. There was an incidence of surgical bleeding of 0.2% (1 of 604) in controls and of 1.7% (13 of 760) with NSAIDs. That difference was statistically significant.
The OR was 4.54 (95% CI, 1.54 –13.42), and the NNH was 65 (95% CI, 40–176).
5 of these 9 studies reported that the bleeding was severe and thus clinically relevant: need for blood transfusion, need for reoperation or defined as “serious postoperative hemorrhage.”
When data from these five trials were combined, there was an incidence of severe surgical bleeding of 0% (0 of 259) in controls and of 1.7% (7 of 410) with NSAIDs. Again, the difference was statistically significant; the odds ratio was 6.08 (95% CI, 1.33–27.86), and the NNH was 59 (95% CI, 34–221).

Conclusion: NSAIDs increased the risk of severe bleeding from 0% to 1.7% (number needed to harm, NNH, 59). No surgical bleeding complications were reported with COX-2 inhibitors.

Table Summary of the RCTs including adult patients included in the systematic review by Riggin *et al.* 2013

	Author, Year	No of patients	NSAID used /Dose	Time/route	Comparison group	Results (NSAIDs versus non-NSAIDs)
1	Dommerby 1984	97	Diclofenac 100 mg, 50 mg at night, 50 mg next morning	Rectal, post-op	Placebo	**Bleeding risk** ↔ Primary bleeding: 3/47 vs 4/50 Secondary bleeding: 2/47 vs 0/50 Bleeding requiring reoperation: 1/47 vs 0/50
2	Kotecha 1991	50	Diclofenac 1 mg/kg	IM, peri-op	Papaveretum	**Bleeding risk** ↔ Blood loss: 100 mL (40-215) vs 110 mL (25–450) Secondary haemorrhage: 0/27 vs 1/23
3	Petruson 1991	96	Diclofenac 50 mg	Rectal, post-op	Paracetamol and codeine (Citodon)	**Bleeding risk** ↔ Post-op haemorrhage: 1/48 vs 1/48

						Bleeding requiring reoperation: 1/48 vs 0/48
4	Rorarius 1993	63	Diclofenac 75 mg Indomethacin 50 mg	IV, peri-op	Placebo	Blood loss: diclofenac 159 g (SD 156.6), indomethacin 157.1 g (SD 130.4) vs 147.7 g (SD 114) 'Bleeding tendency scale, 1 = low, 9 = worst possible state': diclofenac 4.7, indomethacin 4.4 vs 4.3
5	Tarkkila 1999	80	Diclofenac 75 mg Ketoprofen 100 mg Ketorolac 30 mg	IV, peri-op and post-op	Placebo	**Bleeding requiring reoperation** ↔ Blood loss with diclofenac 97 mL (range 10–300), ketoprofen 80 mL (range 10–200), ketorolac 86 mL (range 10–200) vs 71 mL (5–250) Bleeding requiring reoperation: 0/20 vs 2/20
6	Schmidt 2001	80	Diclofenac 0.65–1 mg/kg	Rectal, pre-op	Paracetamol	Mean intra-op blood loss (mL/kg): 1.9 vs 1.1 Bleeding requiring reoperation: 2/40 vs 0/40 Bleeding requiring tranexamic acid: 3/40 vs 0/40
7	Hiller 2004	71	Diclofenac 75 mg	IV, peri-op	Propacetamol, Propacetamol + diclofenac	Mean intraoperative blood loss (mL): diclofenac = 130, propacetamol = 93, combined = 91
8	Nishiike 2007	25	Flurbiprofen 50 mg	IV, pre-op	Placebo	**Bleeding requiring reoperation** ↔ Mean intra-op bleeding (ml): 104 vs 47 Bleeding requiring reoperation: 0/15 vs 0/10
9	Parker 1986	110	Ibuprofen 600 mg	Oral, post-op	ASA, placebo	Haemorrhage: 0/44 vs 0/33
10	Nikanne 2005	115	Ketoprofen, Celecoxib K = 100 mg, C = 200 mg	Oral, pre-op, post-op	Placebo	Mean intraoperative blood loss (mL): celecoxib = 5, ketoprofen = 8, placebo = 20 Primary haemorrhage (electrocautery and current and/or compression and ligation local anaesthetic): ketoprofen = 1/37, celecoxib = 0/39, placebo = 0/39 Secondary haemorrhage (electrocautery and local anaesthetic): ketoprofen = 5/37, celecoxib = 1/39, placebo = 0/39
11	Bailey 1997	80	Ketorolac 30mg	IM Post-op	Meperidine	Post-operative haemorrhage: 7/37 vs 3/43 Bleeding requiring reoperation: 2/37 vs 1/43 Bleeding requiring readmission: 1/37 vs 1/43
12	Isik 2009	40	Lornoxicam 8 mg	IV, pre-op	Tramadol	Above average bleeding: 3/20 vs 4/20

						Profuse bleeding: 2/20 vs 2/20 – neither required medical intervention
13	Ismail 2010	60	Lornoxicam 16 mg	IV, pre-op	Peritonsillar lornoxicam infiltration;	Bleeding 0/20 vs 0/20 infiltration versus 1/20 placebo (excluded from blood loss calculation due to placebo IV extensive bleeding intraoperatively) Blood loss: 84 ` 48 mL Infiltration: 95 ` 52 mL, placebo: 75 ` 44 mL
14	Mowafi 2011	40	Lornoxicam 16 mg	IV, pre-op	Placebo	Mean intraoperative blood loss (mL): 75 vs 54 Bleeding requiring reoperation: 0/20 vs 0/20

LAPSED

Otsing:
((("anti-inflammatory agents, non-steroidal"[Pharmacological Action] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR ("anti-inflammatory"[All Fields] AND "agents"[All Fields] AND "non-steroidal"[All Fields]) OR "non-steroidal anti-inflammatory agents"[All Fields] OR "nsaid"[All Fields]) AND ("hemorrhage"[MeSH Terms] OR "hemorrhage"[All Fields] OR "bleeding"[All Fields])) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]) AND "2005/01/30"[PDat] : "2015/01/27"[PDat] AND "humans"[MeSH Terms] AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]))

1. **Lewis et al.** "Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy." *Cochrane Database Syst Rev* 7 (2013).

Background: NSAIDs are used for pain relief following tonsillectomy in children. However, as they inhibit platelet aggregation and prolong bleeding time they could cause increased perioperative bleeding. The overall risk remains unclear.
Objectives: to assess the effects of NSAIDs on bleeding with paediatric tonsillectomy. Secondary outcome was to establish whether NSAIDs affect the incidence of other postoperative complications when compared to other forms of analgesia.
SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 10); MEDLINE (inception until October 2012); EMBASE (inception until October 2012); Current Problems (produced by the UK Medicines Control Agency), MedWatch (produced by the US Food and Drug Administration) and the Australian Adverse Drug Reactions Bulletins (to May 2010). The original search was performed in August 2004. We also contacted manufacturers and researchers in the field.
SELECTION CRITERIA: We included RCTs assessing NSAIDs in children, up to and including 16 years of age, undergoing elective tonsillectomy or adenotonsillectomy.
DATA COLLECTION AND ANALYSIS: Two authors independently assessed trial quality and extracted the data. We contacted study authors for additional information, where necessary.
RESULTS: We included 15 studies that involved 1101 children in this updated review. One study was added as a result of our 2012 search, another previously included study was removed due to lack of randomization. Fourteen included studies compared NSAIDs with other analgesics or placebo and reported on bleeding requiring surgical intervention. The use of NSAIDs was associated with a non-significant increase in the risk

ofbleeding requiring surgical intervention: Peto odds ratio (OR) 1.69 (95% confidence interval (CI) 0.71 to 4.01). Ten studies involving 365 children reported perioperative bleeding requiring non-surgical intervention. NSAIDs did not significantly alter the number of perioperative bleeding events requiring non-surgical intervention: Peto OR 0.99 (95% CI 0.41 to 2.40) but the confidence intervals did not exclude an increased risk. Thirteen studies involving 1021 children reported postoperative vomiting. There was less vomiting when NSAIDs were used as part of the analgesic regime than when NSAIDs were not used: Mantel Haenszel (M-H) risk ratio (RR) 0.72 (95% CI 0.61 to 0.85).
AUTHORS' CONCLUSIONS: There is insufficient evidence to exclude an increased risk of bleeding when NSAIDs are used in paediatrictonsillectomy. They do however confer the benefit of a reduction in vomiting

2. Cardwell, Siviter and Smith. "Cochrane Review: Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy." Evidence-Based Child Health: A Cochrane Review Journal 7.1 (2012): 244-287.

Background: NSAIDs are used for pain relief following tonsillectomy in children. However, as they inhibit platelet aggregation and prolong bleeding time, they could cause increased perioperative bleeding. The overall risk remains unclear.
This review was originally published in 2004 and was updated in 2010.
Objectives: to assess the effects of NSAIDs on bleeding with paediatric tonsillectomy. Our secondary outcome was to establish whether NSAIDs affect the incidence of other postoperative complications when compared to other forms of analgesia.
Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 6); MEDLINE
(inception until May 2010); EMBASE (inception until May 2010); Current Problems (produced by the UK Medicines Control Agency),
MedWatch (produced by the US Food and Drug Administration) and the Australian Adverse Drug Reactions Bulletins (to May 2010).
The original search was performed in August 2004. We also contacted manufacturers and researchers in the field.
Selection criteria: We included randomized controlled trials assessing NSAIDs in children, up to and including 16 years of age, undergoing elective tonsillectomy or adenotonsillectomy.
Data collection and analysis: Two authors independently assessed trial quality and extracted the data. We contacted study authors for additional information, where
necessary.
Main results: We included 15 trials that involved 1046 children in this updated review. This included one trial that was added as a result of updating our search and another trial that we had incorrectly excluded from our previous review. All included trials compared NSAIDs with other analgesics or placebo and looked at bleeding requiring surgical intervention. NSAIDs did not significantly alter the number of perioperative bleeding events requiring surgical intervention: Peto odds ratio (OR) 1.32 (95% confidence interval (CI) 0.47 to 3.70). Eight trials involving 532 children looked at bleeding not requiring surgical intervention. NSAIDs did not significantly alter the number of perioperative bleeding events not requiring surgical intervention: Peto OR 1.00 (95% CI 0.39 to 2.53).
Authors' conclusions: NSAIDs did not cause any increase in bleeding that required a return to theatre. There was significantly less nausea and vomiting when
NSAIDs were used compared to alternative analgesics

3. Chan and Parikh. "Perioperative ketorolac increases post-tonsillectomy hemorrhage in adults but not children." *The Laryngoscope* (2014).

Objective: To evaluate the risk of post-tonsillectomy hemorrhage associated with perioperative ketorolac use.
STUDY DESIGN: Systematic review and meta-analysis of primary articles reporting individual-level post-tonsillectomy hemorrhage rates in subjects receiving perioperative ketorolac and matched controls. Retrospective and prospective studies were both included.
METHODS: PubMed search was performed for "[ketorolac OR toradol] AND tonsillectomy." Articles fulfilling inclusion criteria were subjected to meta-analysis to determine summary relative risk (RR).
RESULTS: Adults are at five times increased risk for post-tonsillectomy hemorrhage with ketorolac use (RR: 5.64; 95% confidence interval [CI]: 2.08-15.27; P < .001). In contrast, children under 18 are not at statistically significantly increased risk (RR: 1.39; 95% CI: 0.84-2.30; P = .20). Both retrospective and prospective studies yield consistent findings. There is no association of RR with pre- or postoperative administration of ketorolac.
CONCLUSIONS: Ketorolac can be used safely in children, but is associated with a five-fold increased bleeding risk in adults.

RCTs

1. **Moss et al**. "A multicenter, randomized, double-blind placebo-controlled, single dose trial of the safety and efficacy of intravenous ibuprofen for treatment of pain in pediatric patients undergoing tonsillectomy." Pediatric Anesthesia 24.5 (**2014**): 483-489.

Background: Tonsillectomy is one of the most common pediatric procedures in the United States. An optimal perioperative pain control regimen remains a challenge. I/v ibuprofen administered at induction of anesthesia may be a safe and efficacious option for postoperative tonsillectomy pain.
OBJECTIVES: To determine whether preoperative administration of IV-ibuprofen can significantly decrease the number of doses of postop fentanyl when compared with placebo in pediatric tonsillectomy surgical patients.
METHODS: multicenter, randomized, double-blind placebo-controlled trial conducted at 6 hospitals in the United States. A total of 161 pediatric patients aged 6-17 years undergoing tonsillectomy were randomized to receive either a single preoperative dose of 10 mg·kg(-1) IV-ibuprofen or placebo (normal saline). Postoperative pain was managed with iv fentanyl (0.5 µg·kg(-1)) on an as needed basis when the VAS was >30 mm and deemed appropriate by recovery room nurse/physician. The primary endpoint was the number of doses and amount of postoperative fentanyl administered postoperatively for rescue analgesia.
RESULTS: There was a significant reduction in the number of postoperative doses and the amount of fentanyl administered after surgery in the IV-ibuprofen group compared with the placebo group (P = 0.021). There were no differences in the time to first analgesia request or the number of patients who required postoperative analgesia. There were no significant differences in the incidence of serious adverse events, surgical blood loss (P = 0.662), incidence of postoperative bleeding, or a need for surgical re-exploration between the treatment groups.
CONCLUSION: Administration of IV-ibuprofen, 10 mg·kg(-1) , significantly reduced fentanyl use in pediatric tonsillectomy patients.