Non-steroidal anti-inflammatory drugs in treatment of postoperative pain after cardiac surgery

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Purpose: Non-steroidal anti-inflammatory drugs (NSAIDs) are used as analgesic in postoperative pain to reduce opioid side effects, such as drowsiness and nausea. However, NSAIDs have not been used extensively in cardiac surgical patients due to the fear of untoward effects on gastric, renal, and coagulation parameters. This study will evaluate the efficacy and safety of three NSAIDs for pain control in CABG patients.

Methods: One hundred and twenty patients scheduled for elective CABG surgery were enrolled in randomized, double blind, controlled study. Standardized fast track cardiac anesthesia was used. One dose of drug (75 mg diclofenac, 100 mg ketoprofen, 100 mg indomethacin, or placebo) was given *pr* one hour before tracheal extubation and a second dose 12 hr later. Pain was treated with morphine *iv* and acetaminophen *po*. Visual analogue pain scores were recorded at baseline, 3, 6, 12 and 24 hr after the first dose of drug.

Results: There were no differences among the groups in pain scores. Only patients who received diclofenac required less morphine than patients in the control group ($P < 0.05$). When the total amounts of pain medications were computed to morphine equivalents, only patients in the diclofenac group received less pain medications than the placebo group ($P < 0.05$). Proportion of patients with postoperative increase of creatinine level (20% and over) did not differ between placebo and drug groups.

Conclusion: Non-steroidal anti-inflammatory drugs may be used for analgesia management post CABG surgery in selected patients. Diclofenac appears to have the best analgesic effects by reducing the morphine and other analgesic requirement postoperatively.

Objectif : Les anti-inflammatoires non stéroïdiens (AINS) servent d'analgésie postopératoire et réduisent les effets secondaires des opioïdes, comme la somnolence et les nausées. Leur emploi en cardiologie est plutôt restreint où on craint des effets gastriques et rénaux indésirables et des modifications de la coagulation. On a voulu évaluer l'efficacité et la sécurité d'emploi analgésique de trois AINS chez des patients qui subissent un pontage aortocoronarien.

Méthode : L'étude randomisée, contrôlée et à double insu a porté sur 120 patients qui devaient subir un pontage aortocoronarien. Une anesthésie cardiaque normalisée pour un séjour hospitalier écourté a été utilisée. Une dose de médicament (75 mg de diclofénac, 100 mg de kétoprofène, 100 mg d'indométhacine, ou un placebo) a été administrée *pr* une heure avant l'extubation endotrachéale et une seconde dose 12 h plus tard. La douleur a été traitée avec de la morphine *iv* et de l'acétaminophène *po*. Les scores de douleur ont été enregistrés à l'échelle visuelle analogique au début, puis 3, 6, 12 et 24 h après la première dose de médicament.

Résultats : Les scores de douleur n'ont pas présenté de différence intergroupe. Seuls les patients du groupe diclofénac ont demandé moins de morphine que ceux du groupe témoin ($P < 0,05$). Lorsque les quantités totales d'analgésiques ont été calculées en équivalents de morphine, seuls les patients du groupe diclofénac avaient reçu moins d'analgésique que les témoins ($P < 0,05$). La proportion de patients qui présentaient une augmentation postopératoire du niveau de créatinine (20 % et plus) ne différait pas du groupe placebo aux autres groupes.

Conclusion : Les anti-inflammatoires non stéroïdiens sont utiles en analgésie postopératoire chez des patients qui subissent un pontage aortocoronarien planifié. Le diclofénac semble offrir la meilleure analgésie en réduisant les besoins de morphine et d'autres analgésiques.

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EARLY tracheal extubation has been shown to be safe and cost-effective after cardiac surgery.¹⁻³ Fast track cardiac anesthesia requires lower doses of opioids in the peri- and postoperative period. Good postoperative pain control is essential to ensure adequate breathing, as well as to reduce the number of ischemic episodes after coronary artery bypass grafting (CABG) surgery.⁴ The main concern for using high doses of opioids in the postoperative period is the risk for drowsiness and respiratory depression. Opioids have also been associated with other side effects including: confusion, nausea, vomiting, ileus, biliary spasm and urinary retention. Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce morphine requirements in variety of surgical procedures and are devoid of CNS side effects typical of narcotics.⁵⁻⁸ Non-steroidals exert their anti-nociceptive action by blocking the peripheral synthesis of prostaglandins by inhibiting the cyclo-oxygenase enzyme one (COX-1), although a central mechanism has recently been proposed. Non-steroidals also inhibit prostaglandin synthesis by inhibiting the cyclo-oxygenase enzyme two (COX-2) which causes platelet dysfunction, may cause renal impairment by blood flow redistribution in kidneys and are responsible for gastrointestinal symptoms.⁹ Therefore, NSAIDs have not been used widely in cardiac surgical patients due to these concerns. This prospective, randomized, double-blind and placebo-controlled study was designed to evaluate the efficacy and safety (postoperative bleeding, renal function and nausea) of three non-steroidal anti-inflammatory agents; diclofenac, ketoprofen and indomethacin for pain control in CABG patients. The choice of these particular drugs was dictated by our clinical experience with indomethacin used by us for pain control after cardiac surgery,¹⁰ safer profile of diclofenac and widely advertised analgesic property of ketoprofen.

Methods

After Institutional Ethics Committee approval, 120 patients (as calculated for sample size) scheduled to undergo elective coronary artery bypass grafting consented to participate in this study. Patients were instructed preoperatively how to use the visual analogue scale (VAS) for pain. Preoperative exclusion criteria are shown in Table I. Patients were withdrawn from the study if they had prolonged cardiopulmonary bypass (>150 min), required intra-aortic balloon pump support, had postoperative bleeding >100 ml·hr⁻¹, early postoperative creatinine increase > 20%, failure to extubate within nine hours or postoperative stroke.

Patients were randomly allocated to receive 75 mg diclofenac, 100 mg ketoprofen, 100 mg indomethacin or placebo twice *pr* postoperatively in the intensive care unit (ICU). These doses were selected as they were the maximum, equipotent suggested daily doses for these drugs. Randomization and preparation of study drugs into identically shaped suppositories was done by the hospital pharmacy.

Anesthetic management

All patients received standardized fast track cardiac anesthesia.¹² Preoperative sedation consisted of 1-3 mg of lorazepam *sl*. Anesthesia was induced with 10-15 µg·kg⁻¹ fentanyl, 0.15 mg·kg⁻¹ pancuronium bromide 50-100 mg and thiopental. Midazolam, up to 0.1 mg·kg⁻¹, and isoflurane 0.4-1.5% were used for maintenance of anesthesia before CPB. Propofol infusion of 2-6 mg·kg⁻¹·hr⁻¹ was commenced at the start of cardiopulmonary bypass. All patients received tranexamic acid (50 mg·kg⁻¹) after anesthesia induction as per routine in our Institution.

Patients underwent a median sternotomy. Saphenous veins and internal thoracic artery were used as conduits for coronary artery bypass. Patients were not actively cooled but temperature was allowed to drift during cardiopulmonary bypass. Patients were warmed to nasopharyngeal temperature of 37-38°C before termination of cardiopulmonary bypass.

Management in the ICU

Propofol was continued in the ICU at a rate of 1-4 mg·kg⁻¹·hr⁻¹ until the patients reached tracheal extubation criteria.¹² Patients should be hemodynamically stable, have reached a rectal temperature of 36°C and not bleeding excessively. Neuromuscular blockade was reversed with 2.5 mg neostigmine and 0.4 mg glycopyrrolate or 1.2 mg atropine before discontinuation of the propofol infusion.

Shivering was treated with 12.5-50 mg meperidine. Hypertension was treated with nitroglycerin or sodium nitroprusside *iv*. The first dose of the study drug was given *pr* 60 min before the estimated time of extubation. A second dose of the same study drug was given 12 hr after the initial dose. The tracheas were extubated if the patients were awake, followed commands, were able to create a negative inspiratory force of -20 cmH₂O and a vital capacity of >10 ml·kg⁻¹. Further pain was treated with 2 mg morphine *iv* repeated every five minutes until pain score was 3 (up to 30 mg in four hours) in the immediate postoperative period by the attending ICU nurse. Patients were transferred to the surgical floor on the first postoperative day if they were hemodynamically stable. Pain

was treated there at request with tablets of Tylenol #3® (325 mg acetaminophen plus 30 mg codeine), Percocet® (325mg acetaminophen plus 5 mg oxycodone) or Tylenol (325 mg acetaminophen) if patients were allergic to codeine. The total analgesic consumption was calculated as morphine equivalents according to the following formula:

$$\text{Morphine equivalent (mg)} = [\text{meperidine(mg)} / 75(10)] + [(\text{No of Tylenol\#3 tablets}) (30/200(10))] + [(\text{No of Percocet tablets}) (5/15(10))] + [\text{No of Tylenol tablets}/3900(10)] + \text{morphine(mg)}.$$

Morphine equivalents were calculated based on opioid and analgesic comparison in Compendium of Pharmaceuticals and Specialities, 33th ed. 1998. Canadian Pharmacist Association, Ottawa, Ontario, Canada.

A VAS was used to evaluate the efficacy of the pain management. The VAS score at rest was estimated by the patient preoperatively and 3, 6, 12 and 24 hr after the first dose of the study drug. Total morphine consumption and other pain medications were recorded during the first 24 hr. Nausea was treated with 12.5-25 mg dimenhydrinate *iv*. The incidence of nausea and vomiting was recorded. Urine output, use of diuretics and chest tube blood loss was recorded during the first 24 hr. Serum creatinine level was measured daily until the patients were discharged.

TABLE I Preoperative exclusion criteria

Ejection fraction <20%
Previous cardiac surgery
Insulin dependent diabetes mellitus
Weight >100 kg or <60 kg
Renal insufficiency (creatinine >130 $\mu\text{mol}\cdot\text{L}^{-1}$)
Allergy to propofol, morphine or any NSAID
Active peptic ulcer disease, history of gastrointestinal bleeding
Age >75 yr
Warfarin, dipyridamole or heparin therapy preoperatively

Statistical analysis

Data are presented as mean $\pm$ SD unless indicated otherwise. Demographic data among groups were compared by one-way ANOVA and posthoc Tukey test. Data on doses of the analgesics were logarithmically transformed to achieve normal distribution. Mean values were compared between each drug group and the placebo by one-way ANOVA and posthoc Dunnett test. Ninety five percent confidence intervals were calculated. Thereafter mean values were recalculated to mg of drug and presented as mean and CI.95. The VAS scores were analyzed by Kruskal-Wallis test for independent k sample. Median values were calculated. Frequencies were compared using Chi-square statistics.

The sample size was calculated for comparison of each drug group to placebo with respect to morphine sparing property. To reduce the number of patients per group there was no planned comparison among the drug groups. To detect 7.5 mg difference in 24 hr morphine consumption with 7.5 mg SD we needed 25 subjects per group. (α 0.05 and β 0.8). The sample size for assessing renal function postoperatively were calculated on following basis: after uncomplicated CABG, 15% of patients not treated with NSAIDs suffer considerable (20% and over) increase in creatinine level postoperatively. To detect 50% increase (from 15 to 30%) in patients with increased postoperative creatinine by 20% we needed 75 patients in the NSAIDs group and 25 patients in placebo (α 0.05, β 0.8). To detect an increase in postoperative blood loss by a mean value of 200 ml (SD=200 ml) we needed 50 patients in the NSAIDs group compared to 25 patients in the control group (α =0.05 and β 0.8).

Results

One hundred and fourteen patients completed the study and were in the final analysis of the data. Six patients were withdrawn from the study. In one

TABLE II Demographic and preoperative clinical data (mean $\pm$ SD)

	<i>Diclofenac</i> (n=28)	<i>Ketoprofen</i> (n=28)	<i>Indomethacin</i> (n=27)	<i>Placebo</i> (n=31)
Age (yr)	59 $\pm$ 9	60 $\pm$ 7	58 $\pm$ 9	55 $\pm$ 9
Sex (male/female)	20 / 8	24 / 4	21 / 6	28 / 3
Weight (kg)	78 $\pm$ 12	78 $\pm$ 9	79 $\pm$ 10	81 $\pm$ 10
ASA _a II/III/IV	0/21/5	1/23/3	1/24/2	1/29/0
LV _b grade 1/2/3/4	8/10/6/0	9/11/3/0	10/9/6/0	9/15/4/1
NIDDM _c	2/28	6/28	3/27	3/31
Hemoglobin (g·L ⁻¹)	136 $\pm$ 13	140 $\pm$ 12	137 $\pm$ 10	139 $\pm$ 15
Creatinine ($\mu\text{mol}\cdot\text{L}^{-1}$)	86 $\pm$ 13	83 $\pm$ 10	84 $\pm$ 17	90 $\pm$ 16

_a American Society of Anesthesiologist, _b Left Ventricular, _c Non insulin dependant diabetes mellitus

TABLE III Intraoperative clinical data (mean $\pm$ SD)

	<i>Diclofenac</i>	<i>Ketoprofen</i>	<i>Indomethacin</i>	<i>Placebo</i>
ACT* (prebypass) sec	145 $\pm$ 18	144 $\pm$ 18	152 $\pm$ 20	144 $\pm$ 20
ACT (postbypass) sec	153 $\pm$ 41	142 $\pm$ 23	139 $\pm$ 36	139 $\pm$ 44
CPB† time (min)	85 $\pm$ 29	82 $\pm$ 23	86 $\pm$ 31	97 $\pm$ 23
Cross-clamp time (min)	62 $\pm$ 19	60 $\pm$ 19	62 $\pm$ 21	65 $\pm$ 16
Lowest CPB temp °C	33 $\pm$ 2.3	34 $\pm$ 0.6	34 $\pm$ 0.7	34 $\pm$ 0.6
Lowest CPB hematocrit	0.23 $\pm$ 0.03	0.23 $\pm$ 0.03	0.23 $\pm$ 0.03	0.24 $\pm$ 0.04
Tranexamic acid dose (g)	3.8 $\pm$ 1.0	3.7 $\pm$ 1.3	4.0 $\pm$ 0.9	3.9 $\pm$ 1.4

* Activated coagulation time, † Cardiopulmonary bypass

TABLE IV Postoperative data

	<i>Diclofenac</i>	<i>Ketoprofen</i>	<i>Indomethacin</i>	<i>Placebo</i>	<i>Signific.</i>
Chest tube loss (ml)	560 $\pm$ 260	630 $\pm$ 200	530 $\pm$ 230	580 $\pm$ 230	NS
$\geq$ 20% increase in creatinine		5 (6.3%)		1 (3.5 %)	NS
S- creatinine $\mu\text{mol}\cdot\text{L}^{-1}$ POD* 1	73 $\pm$ 10	81 $\pm$ 19	74 $\pm$ 14	78 $\pm$ 16	NS
S- creatinine $\mu\text{mol}\cdot\text{L}^{-1}$ POD 3	81 $\pm$ 11	84 $\pm$ 12	84 $\pm$ 18	80 $\pm$ 16	NS
Nausea (% of patients)	46%	36%	26%	29%	NS
Vomiting (% of patients)	29%	18%	19%	13%	NS

* postoperative day

patient in the indomethacin group (given one dose of drug) postoperative serum creatinine increased to 137 from 105 postoperatively and normalized on discharge. Another patient in the indomethacin group had excessive bleeding coincidentally with the first dose of indomethacin and was not given the second dose. The bleeding was managed conservatively. In three patients the tracheas were not extubated within the designated time limit and were withdrawn from the study. One patient suffered from a postoperative stroke and was also withdrawn.

The groups were comparable in terms of clinical preoperative and intraoperative data (Tables II, III). Postoperatively there were no differences among the groups in postoperative creatinine concentration, percentage of patients with 20% and over increase in creatinine level postoperatively and 24 hr blood loss (Table IV). There were no chest re-explorations for bleeding. The VAS pain scores at rest were comparable among the four groups at all times (Figure 1).

Mean morphine consumption in the 24 hr postoperatively was reduced only in the diclofenac group when compared with placebo, mean 12.4 mg (8.9-16mg 95% CI) *vs* 19 mg (14.8-23.2 95% CI), ($P < 0.05$). Total analgesic consumption calculated as morphine equivalents was also lower only in the diclofenac group when compared with placebo, mean 18.1 mg (13.4-22.8 95% CI) *vs* 26.5 mg (22.8-31.5 mg), ($P < 0.05$). No difference was seen when doses of other analgesics were compared among drugs and placebo group. (Figure 1)

FIGURE 1 Visual Analog Scale (VAS) at 3, 6, 12, 24 hr post administration of 1st dose of

Discussion

We have demonstrated that the non-steroidal anti-inflammatory drug, diclofenac may be used in selected cardiac surgical patients to reduce the amount of opioid medication in the immediate postoperative period. Diclofenac has an additional advantage because its safety profile is better than that of indomethacin and it is much cheaper than ketoprofen. The pain scores were low in the diclofenac group except at 12 hr after the first dose of the drug. This may be because elimination half-life of diclofenac is relatively short (5.1 hr) and that might have warranted dosing of diclofenac at eight-hour intervals.

FIGURE 2 Consumption of morphine and morphine equivalent
 Group 1 = Diclofenac
 Group 2 = Ketoprofen
 Group 3 = Indomethacin
 Group 4 = Placebo
 Diclofenac group compared to placebo group; decrease in morphine consumption $P = 0.05$, decrease in morphine equivalent $P = 0.05$.
 (morphine equivalent = morphine + tylenol + codeine + oxycodone)

The major theoretical advantages in using NSAIDs for postoperative pain would be to avoid respiratory depression, drowsiness and to produce a more stable anti-analgesic effect than iv morphine, which is the standard postoperative management after cardiac surgery. In contrast to the dose-dependent analgesic effects of opioid analgesics, NSAIDs appear to exhibit a ceiling effect with respect to analgesia. Due to the limited analgesic effect the NSAIDs can be used only as adjuncts for opioid therapy.

In our study, we did not observe any serious side-effects in terms of increased postoperative blood loss apart from one patient in the indomethacin group which could be coincidental. None of our patients developed GI-bleeding but we did see an increase of nausea and vomiting in patients receiving NSAIDs than in the placebo group. This may be precipitated by stomach upset induced by NSAIDs in most of the patients. In respect to renal function only one patient experienced increased creatinine concentration after doses of indomethacin but not after two other NSAID used in the study. We compared the proportion of patients who had an increase in their creatinine levels of 20% and more from the preoperative level and we did not detect any difference comparing all patients receiving NSAIDs and placebo. (Table IV) This is not absolute proof of safety of these drugs in respect to kidney function (such a study would required 5000 patients per group to be studied) but it is reassuring that two doses of NSAIDs in a selected group of

patients does not induce severe renal dysfunction postoperatively.^{10,11} However, because of the remote possibility of side effects inherent in the action of NSAIDs we limited the category of patients in whom we would administer NSAIDs after cardiac surgery as per our study requirements. (Maximum two doses of NSAIDs, excluding patients >75 yr, diabetics, patients with elevated creatinine concentration or with a history of peptic ulcer.)

The limitation of this study was that we did not use PCA morphine for postoperative pain control, as the administration of analgesics by the nurse might have affected the results. However, these patients were nursed on 1:1 ratio until they were discharged to the surgical floor and that consumption of morphine is not different when PCA is compared with nurse titrated analgesia after cardiac surgery.¹²

In respect to nausea and vomiting it would be interesting to see if short term use of H_2 inhibitors or antacids would change the frequency of nausea and vomiting in patients receiving NSAIDs in the postoperative period.

Conclusion

Non-steroidal anti-inflammatory drugs may be used as an adjunct for analgesia management post CABG surgery in selected patients. Diclofenac appears to have the best analgesic effect by reducing morphine and other analgesic requirement postoperatively. Diclofenac should be administered every eight hours to a maximum of 150 mg in 24 hr.

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