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Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children

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Background. Caudal block is a common technique for paediatric analgesia but with the disadvantage of short duration of action after single injection. Caudal dexmedetomidine and clonidine could offer significant analgesic benefits. We compared the analgesic effects and side-effects of dexmedetomidine and clonidine added to bupivacaine in paediatric patients undergoing lower abdominal surgeries.

Methods. Sixty patients (6 months to 6 yr) were evenly and randomly assigned into three groups in a double-blinded manner. After sevoflurane in oxygen anaesthesia, each patient received a single caudal dose of bupivacaine 0.25% (1 ml kg^{-1}) combined with either dexmedetomidine 2 $\mu g\ kg^{-1}$ in normal saline 1 ml, clonidine 2 $\mu g\ kg^{-1}$ in normal saline 1 ml, or corresponding volume of normal saline according to group assignment. Haemodynamic variables, end-tidal sevoflurane, and emergence time were monitored. Postoperative analgesia, use of analgesics, and side-effects were assessed during the first 24 h.

Results. Addition of dexmedetomidine or clonidine to caudal bupivacaine significantly promoted analgesia time [median (95% confidence interval, CI): 16 (14–18) and 12 (3–21) h, respectively] than the use of bupivacaine alone [median (95% CI): 5 (4–6) h] with $P<0.001$. However, there was no statistically significant difference between dexmedetomidine and clonidine as regards the analgesia time ($P=0.796$). No significant difference was observed in incidence of haemodynamic changes or side-effects.

Conclusions. Addition of dexmedetomidine or clonidine to caudal bupivacaine significantly promoted analgesia in children undergoing lower abdominal surgeries with no significant advantage of dexmedetomidine over clonidine and without an increase in incidence of side-effects.

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Caudal epidural block is one of the most popular, reliable, and safe techniques in paediatric analgesia that can provide analgesia for a variety of infra- and supraumblical surgical procedures. The main disadvantage of caudal analgesia is the short duration of action after a single injection.[1] The use of caudal catheters to administer repeated doses or infusions of local anaesthetics is not popular, partly because of concerns about infection. Prolongation of caudal analgesia using a 'single-shot' technique has been achieved by the addition of various adjuvants, such as epinephrine, opioids, ketamine, and α_2 agonists.[2]

Clonidine action, similar to local anaesthetic action, and its interaction with local anaesthetics have been explained by three possible mechanisms. First, clonidine blocks Aδ and C fibres as a consequence of an increase in potassium conductance in isolated neurones, thus intensifying local anaesthetic conduction block.[3] Secondly, clonidine may cause local vasoconstriction, thus decreasing local anaesthetic spread and removal around neural structures. This effect is mediated by drug action on post-synaptic α_2 receptors, although there is little evidence of this mechanism with clinical doses.[4] Thirdly, clonidine combined with

spinal local anaesthetics or used in peripheral blocks intensifies and prolongs analgesia.[5] Spinal α_2 adrenergic agonists may also induce analgesia by activating spinal cholinergic neurones resulting in acetylcholine release.[6]

Dexmedetomidine has an eight-fold greater affinity for α_2 adrenergic receptors than clonidine and much less α_1 effects. A major advantage of dexmedetomidine is its higher selectivity compared with clonidine for α_{2A} receptors, responsible for the hypnotic and analgesic effects of such drugs.[7–9]

This study was designed to compare the analgesic effects and side-effects of dexmedetomidine and clonidine when added to bupivacaine for caudal analgesia in children undergoing lower abdominal surgeries.

Methods

After local ethical committee approval and obtaining informed parental consent, 60 ASA status I and II patients, aged 6 months to 6 yr undergoing lower abdominal surgeries, were prospectively enrolled in this study.

Study exclusion criteria included a history of developmental delay or mental retardation, which could make observational pain intensity assessment difficult; a known or suspected coagulopathy; a known allergy to any of the study drugs; and any signs of infection at the site of the proposed caudal block.

Using a computer-generated list, the subjects were randomly and evenly assigned into three groups: A, B, and C. All health-care personnel providing direct patient care, the subjects, and their parents or guardians were blinded to the caudal medications administered. All medications were prepared by pharmacy staff not participating in the study except for preparing the drugs. They received and kept the computer-generated table of random numbers according to which random group assignment was performed. After obtaining subjects weight, and according to the randomizing table, the volume to be injected in the caudal block was prepared in syringes with labels indicating only the serial number of the patient.

All subjects received a conventional preoperative dose of oral midazolam (0.5 mg kg^{-1}) 20–30 min before anaesthetic induction, and then underwent a standard inhalation induction with sevoflurane in oxygen followed by insertion of an i.v. canula and administration of a neuromuscular blocking agent to facilitate endotracheal intubation. Induction was strictly inhalation and atropine was not administered routinely. After endotracheal intubation, patients were placed in the lateral decubitus position, and a single-dose caudal block was performed according to the group under sterile conditions using a 23 G needle and standard loss of resistance technique.

Group 'A' received: bupivacaine 0.25% (1 ml kg^{-1}) with dexmedetomidine 2 μg kg^{-1} in normal saline 1 ml; Group 'B' received: bupivacaine 0.25% (1 ml kg^{-1}) with clonidine 2 μg kg^{-1} in normal saline 1 ml; and Group 'C' received: bupivacaine 0.25% (1 ml kg^{-1}) with normal saline 1 ml, with a maximum volume of 30 ml for all three groups.

General anaesthesia was maintained with sevoflurane delivered in oxygen. The inhaled concentration of sevoflurane was adjusted to achieve haemodynamic changes <30% of the baseline values. No other narcotics, analgesics, sedatives, or antiemetics were administered intraoperatively. At the conclusion of surgery, the patient was awakened and transported to the post-anaesthetic care unit (PACU).

Standard monitoring was used during anaesthesia and surgery. Heart rate and arterial pressure were recorded before operation and every 5 min until the end of surgery. The occurrence of intraoperative hypotension requiring a fluid bolus, bradycardia requiring atropine, and the maximum maintenance end-tidal concentration of sevoflurane (%) were recorded. Perioperative blood loss was replaced meticulously using crystalloids and blood, as appropriate. The anaesthesia time (the time from induction of anaesthesia to the end of surgery when the inhalation agent was discontinued), emergence time (the time from the end of surgery to opening the eyes on calling the patient's name), a delayed anaesthetic emergence (defined as >20 min elapsing from the end of surgery to exiting the operating theatre), or all were also noted.

Using the paediatric observational FLACC pain scale with its 0–10 score range (Table 1),[10] each study participant's pain intensity was assessed upon arrival in and at the time of discharge from the PACU, and then every 4 h for the first 24 h after operation. If the FLACC pain scale score was noted at any time to be 4 or more, morphine 0.2 mg kg^{-1} i.m. was administered to achieve an FLACC scale score of 3 or less. The duration of adequate caudal analgesia (from the time of caudal injection to the first time the FLACC pain scale score was noted to be 4 or more) was also recorded.

Once transferred to the in-patient care unit, the oxygen saturation, heart rate, and arterial pressure were continuously monitored in the presence of a staff nurse. The occurrence of postoperative respiratory depression (defined as oxygen saturation of <95%), hypotension (defined as systolic arterial pressure <70 plus twice the age in years and associated with altered peripheral perfusion), bradycardia (defined as heart rate below 80 beats min^{-1} for ages <1 yr and <60 beats min^{-1} for ages above 1 yr) requiring medical intervention, or all was also noted. Postoperative nausea and vomiting (PONV) was treated as needed with i.v. ondansetron 0.06 mg kg^{-1} every 4 h, postoperative pruritis was treated as needed with i.v. diphenhydramine 0.2 mg kg^{-1} every 6 h.

Postoperative recordings also included: the duration of PACU stay, time of first administration of morphine for each patient, occurrence and treatment of PONV and pruritis, time to first micturition after caudal injection, and the incidence of bladder catheterization. The initiation of clear liquid and solid oral intake and time of discharge home were also recorded.

Table 1 The FLACC pain scale[10]

Categories	Scoring		
	0	**1**	**2**
Face	Smile or no particular expression	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers occasional complaint	Crying steadily screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or talking to, distractable	Difficult to console

Statistical analysis

Calculation of sample size revealed that at least 15 subjects in each group were needed to detect a difference in the average time to first analgesics as small as 1.5 times its standard deviation with a power of 0.9 and a significance level (α) of 0.05.[11] The sample size was increased by 30% (i.e. 20 patients in each group) as the distribution of the primary outcome variable (time to first analgesics) was expected to be skewed (or generally not normally distributed) with the possibility of existence of censored data.

Data were analysed using SPSS® version 12.0 computer software (Chicago, IL, USA). Numerical variables were presented as mean and standard deviation (SD) and categorical variables were presented as frequency (%). One-way ANOVA was used for between-group comparisons of numerical variables, if its assumptions were fulfilled, otherwise for non-parametric, the Kruskal–Wallis test was used. Tukey's HSD test or the Mann–Whitney test was used, whenever appropriate, as *post hoc* tests. χ^2 test was used for between-group comparisons between categorical variables. Time to first analgesic administration was analysed by the Kaplan–Meier survival analysis and log-rank test. A Bonferroni correction of the significance level was applied, if multiple comparisons were indicated. A P-value of <0.05 was considered statistically significant.

The power of the log-rank test was found to be >0.83 for detecting the difference between median survival times of 12 and 5 h during an observation period of 24 h at $\alpha=0.05$. But, it was relatively low (0.13) for comparing median survival times of 12 and 16 h during the same period.

Results

None of the 60 attempted caudal blocks was perceived as being a failed attempt; subject characteristics and intraoperative clinical profile were comparable among the three study groups (Table 2). Specifically, no significant difference was observed between the groups in the average maximum maintenance end-tidal concentration of sevoflurane; incidence of delayed emergence; or the average anaesthesia emergence time. The magnitude of haemodynamic changes between the groups was comparable (Table 2), and therapeutic interventions were not required.

There was a significant difference between the groups in the FLACC score measured 4 h after discharge from the PACU (Fig. 1). Group C patients achieved significantly higher FLACC score compared with Groups A and B, where 30% of patients achieved a FLACC score of 4 compared with 0% and 5% in Groups A and B, respectively.

During the first 4–6 h after operation, all children had adequate caudal analgesia. Subsequently, the number of patients with adequate analgesia in Group C declined much more rapidly than Groups A and B and the differences were statistically significant. The postoperative analgesia time recorded a median of 5 h and 95% confidence interval (CI) (4–6 h) in Group C compared with 16 (14–18) and 12 (3–21) h in Groups A and B, respectively, with a P-value of <0.001 (Table 3 and Fig. 2).

The mean PACU stay was comparable between the groups as were the incidence of pruritis, diphenhydramine requirements, number of PONV, and ondansetron requirements ($P=0.246$, 0.765, 0.596, 0.812, and 0.788, respectively) (Table 4). Mean times to first micturition were 8.1, 7.6, and 8.3 h in Groups A, B and C, respectively. One child in Group C required catheterization and one child in Group A and two in Group B complained of difficulty with micturition but did not require catheterization.

The time to first oral clear liquid intake and first oral solid intake was comparable among the three study groups. There was no observed significant group difference in the time to discharge home (Table 4). No episodes of clinically significant postoperative respiratory depression, hypotension, or bradycardia were observed.

Discussion

The analgesic action of intrathecal or epidural clonidine was first demonstrated clinically in 1984.[12] The successful use of epidural clonidine in adults led to its evaluation in paediatric caudal block. The resulting studies have

Table 2 Subject characteristics and intraoperative clinical data. Values reported as mean (range), mean (SD) or as frequency (%). *Colonic surgery included: resection and bypass. †Intra-abdominal mass: e.g. neuroblastoma and teratoma

	Group A	Group B	Group C	*P*-value
Age (months)	40 (8–60)	45 (6–69)	43 (7–66)	0.706
Weight (kg)	14 (5.2)	16 (4.9)	15 (4.4)	0.450
Female	9 (45%)	8 (40%)	10(50%)	0.817
Type of surgery				
Colonic surgery*	8	6	9	0.630
Bladder augmentation	5	7	4	
Ureteric reimplantation	1	4	2	
Intra-abdominal mass†	3	3	2	
Hepatobiliary surgery	3	0	3	
Anaesthesia time (min)	195 (34)	183 (39)	179 (42)	0.398
End-tidal sevoflurane	2.4 (0.7)	2.4 (0.8)	2.6 (0.7)	0.98
Delayed emergence	0(0%)	1 (5%)	1(5%)	0.596
Emergence time (min)	12.9 (7.2)	12.3 (6.8)	9.1 (3.4)	0.111
MAP (mm Hg)				
Before operation	82.0 (4.5)	79.0 (4.2)	80.0 (4.6)	0.103
Maximal decrease magnitude	18.4 (5.1)	18.0 (4.6)	17.9 (4.7)	0.941
Time (min) after caudal injection	68 (10.4)	70 (9.8)	64 (11.5)	0.198
Heart rate (beats min^{-1})				
Before operation	107.0 (8.6)	105.0 (9.4)	110.0 (8.6)	0.209
Maximal decrease magnitude	18.6 (6.4)	20.8 (5.8)	19.1 (6.6)	0.513
Time (min) after caudal injection	82 (12.5)	85 (13.4)	78 (11.8)	0.219

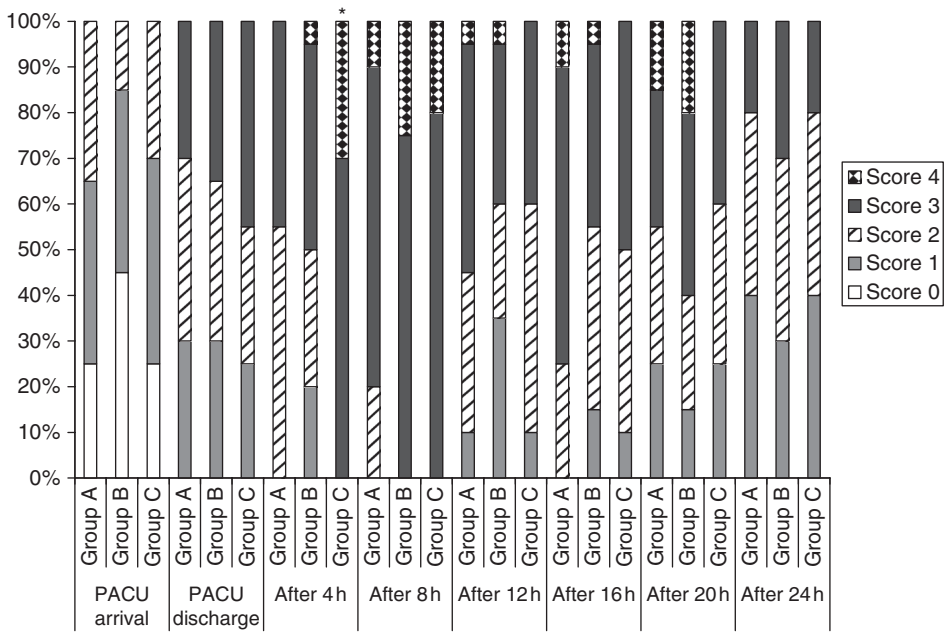

Fig 1 The recorded FLACC scores of the three groups. *Significantly higher than the other two groups.

consistently shown caudal clonidine to increase the duration of postoperative analgesia.[13 14] On the other hand, dexmedetomidine, although currently available for i.v. use only, has been successfully administered epidurally for postoperative analgesia in humans in clinical trials.[15–18] Nevertheless, there are still some concerns regarding its safety.[19]

In this study, we found that the time of adequate caudal analgesia (FLACC scale score <4) without the need for morphine is significantly higher in the groups receiving the bupivacaine–dexmedetomidine mixture [median (95% CI):16 (14–18) h] or bupivacaine–clonidine mixture [median (95% CI): 12 (3–21) h] than the group receiving plain bupivacaine [median (95% CI): 5 (4–6) h].

These results are similar to those reported in a study conducted on children aged 6 month to 9 yr undergoing bilateral correction of vesicoureteral reflux where clonidine 1.5 $\mu g\ kg^{-1}$ was administered caudally with an equal combination of bupivacaine 0.25% and lidocaine 1%.[20] The duration of analgesia in the clonidine group was significantly longer than in the local anaesthetic alone group [mean (SD): 257 (118) and 164 (30) min, respectively; $P=0.035$].

Table 3 Postoperative analgesia data: time of maintaining adequate caudal analgesia (FLACC scale score <4) without the need for morphine. *Significant shorter time when compared with the other two groups. Groups A and B showed no significant difference (P=0.796)

	Group A	Group B	Group C	*P*-value
Time (h): median (95% CI)	16 (14–18)	12 (3–21)	5 (4–6)*	<0.001

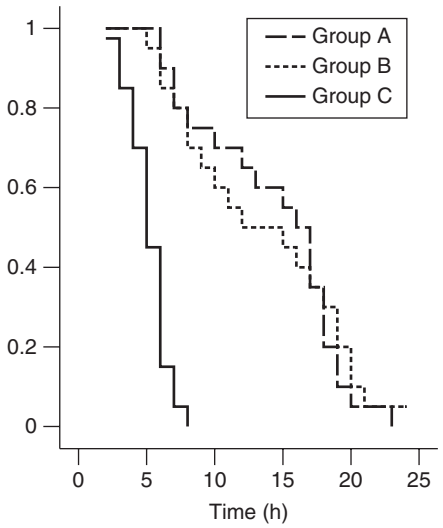

Fig 2 Kaplan–Meier survival curve of time to first analgesic administration.

In another study, patients submitted to total hip replacement received epidural infusion at 6 ml h^{-1} of either levobupivacaine 0.125%, levobupivacaine 0.125% plus clonidine 8.3 μg ml^{-1}, or clonidine alone 8.3 μg ml^{-1}. The median time for first analgesic request was longer in the group receiving clonidine and levobupivacaine (12.5 h) when compared with those receiving pure levobupivacaine or clonidine alone (2.9 and 5.9 h, respectively; P<0.01).[21]

In patients undergoing inguinal hernia correction, the combination of spinal clonidine–bupivacaine prolonged anaesthesia duration and promoted better analgesia observed 4 h after the block.[22] In combination with ropivacaine for caudal block, addition of clonidine 2 μg kg^{-1} to ropivacaine 0.1% (1 ml kg^{-1}) resulted in better postoperative analgesia than ropivacaine 0.2% alone (1 ml kg^{-1}). This combination was not associated with significant sedation or motor block.[23]

In a more recent study, clonidine was caudally administered with bupivacaine 0.125% in a group of children aged 1–10 yr undergoing ureteroneocystostomy.[24] Patients in the clonidine–bupivacaine group required significantly less i.v. morphine during the initial 24 h postoperative period (0.02 mg kg^{-1} in PACU and 0.1 mg kg^{-1} on first postoperative day) than those receiving bupivacaine alone (0.05 mg kg^{-1} in PACU and 0.2 mg kg^{-1} on first postoperative day). Mean interval from anaesthesia finish time to first administered dose of morphine was 8.0 h for the clonidine group and 3.9 h for controls (P=0.01). However, in addition to an initial 1 μg kg^{-1} dose, a second 0.5 μg kg^{-1} dose of clonidine was administered caudally at the conclusion of surgery. Patients also received i.v. ketorolac at the time of wound closure and for the duration of the study. These differences in study design make comparisons with our findings difficult.

Despite ample published evidence supporting the analgesic benefits of clonidine as a caudal additive,[25] at least three studies have failed to observe any such benefit.[26–28] Specifically, in a group of 2–8-yr-old outpatients undergoing urogenital surgery, the addition of clonidine 2 μg kg^{-1} to bupivacaine 0.125% (1 ml kg^{-1}) and epinephrine 1:200 000 did not significantly delay the time to first rescue analgesic or decrease the overall need for rescue analgesics compared with patients receiving bupivacaine 0.125% (1 ml kg^{-1}) and epinephrine 1:200 000 alone.[27] In a randomized study using lidocaine and dexmedetomidine alone or in association, decreased EEG delta wave, arterial pressure, and heart rate were observed in the group receiving dexmedetomidine alone. In the group receiving both drugs, longer anaesthetic duration and decreased analgesic doses for postoperative pain relief were observed.[29] In a recent study conducted on 60 ASA I patients 1–6 yr old undergoing unilateral inguinal hernia repair/orchiopexy, subjects received either caudal bupivacaine 2.5 mg ml^{-1}

Table 4 Postoperative side-effects and rehabilitation data. Values reported as mean (SD) or as frequency (%)

	Group A	Group B	Group C	*P*-value
PACU duration (min)	68 (14.7)	72 (11.3)	65 (13.1)	0.246
Pruritis	1 (5%)	1 (5%)	2 (10%)	0.765
Diphenhydramine	0 (0%)	1 (5%)	1 (5%)	0.596
PONV (no.)	9 (45%)	8 (40%)	7 (35%)	0.812
Ondansetron	6 (30%)	7 (35%)	5 (25%)	0.788
Time to micturition (h)	8.1 (3.4)	7.6 (2.9)	8.3 (3.1)	0.769
Urinary retention (h)	0 (0%)	0 (0%)	1 (5%)	0.362
Clear liquid intake (h)	4.2 (2.6)	4.9 (2.8)	4.5 (2.8)	0.720
Solid intake (h)	23 (12)	24 (11)	22 (9)	0.841
Discharge home	49 (10)	46 (9)	48 (13)	0.672

alone, 1 ml kg^{-1}, or bupivacaine (same dose) mixed with dexmedetomidine 1 μg kg^{-1} during sevoflurane anaesthesia. The duration of analgesia was significantly longer ($P<0.001$) and the total consumption of rescue analgesic was significantly lower ($P<0.01$) in the group receiving bupivacaine–dexmedetomidine than in the group receiving bupivacaine alone.[18]

The addition of dexmedetomidine or clonidine to bupivacaine in this study did not result in an increase in the incidence of side-effects or significantly delay recovery from general anaesthesia. Moreover, the magnitude of haemodynamic changes between the groups was similar. There were no detectable differences in the mean PACU duration, the incidence of pruritis, diphenhydramine requirements, PONV, ondansetron requirements, mean times to first micturition, or the time to first oral clear liquid intake or first oral solid intake. No episodes of clinically significant postoperative respiratory depression, hypotension, or bradycardia were identified. However, we did not assess sedation which is a common side-effect of α_2 adrenergic agonists. We found it difficult to distinguish between sedation and analgesia in this age group, since all the patients were asleep provided they were comfortable and they became restless or awake only when they were in pain and required analgesia.

In a similar study, the addition of clonidine 2 μg kg^{-1} to bupivacaine 0.25% (1 ml kg^{-1}) significantly improved caudal analgesia compared with that provided by bupivacaine alone, without an increase in the incidence of side-effects in children undergoing orthopaedic surgery.[30] However, in another study, the addition of clonidine 150 μg or dexmedetomidine 2 μg kg^{-1} to ropivacaine 0.75% (20 ml) administered in the epidural space in patients undergoing upper abdominal surgery caused a decrease in systemic systolic pressure of 25% of the clonidine group and of 30% in the dexmedetomidine group.[17]

In this study, we used the FLACC Pain Scale. Previous studies of paediatric postoperative caudal analgesia have alternatively used the Children's Hospital of Eastern Ontario Pain Scale,[28] the Children and Infants Postoperative Pain Scale,[31] or the Objective Pain Scale.[32] However, several of these studies observed no significant difference in postoperative observational pain score.[33 34] The underlying issue may be the reported discordance between self-reported and behavioural pain measures in children aged 3–7 yr after surgery.[35]

Our results allow us to conclude that addition of dexmedetomidine (2 μg kg^{-1}) or clonidine (2 μg kg^{-1}) to caudal bupivacaine 0.25% at 1 ml kg^{-1} significantly promoted analgesia after anaesthetic recovery in children aged 6 months to 6 yr, undergoing lower abdominal surgeries without increasing the incidence of side-effects. Moreover, dexmedetomidine did not offer significant advantage over clonidine as regards the analgesia duration.

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