Minireview Article

MECHANISM OFACTION,CELLULARTARGETSANDCLINICALADVANTAGEORDISANVANTAGEOFANALGETICTHERAPYINPOST-OPERATIVEPEDIATRICPATIENTS:ABRIEFREVIEW

ABSTRACT

Pain is a distressing sensation that can cause alterations in several bodily systems,particularly in pediatric children after surgery. Efficient pain treatment is crucial for individualsseeking to minimize or eliminate pain and discomfort while experiencing minimalsideeffects. The objective of this study is to examine the mechanism of action, cellular targets,and clinical result of pain relief treatment in pediatric surgical patients after an operation. Theliterature search for this review was conducted using the Pubmed and Google Scholardatabases, resulting in the acquisition of 30 publications as references. The authors of thisreview have included three categories of analgesic drugs: Acetaminophen, NSAIDs, andopioids. These categories are compared using three specific indicators, as stated in the aimof the review. This concise study demonstrated unanimous agreement among researchersand clinicians that the preferred approach to postoperative analgesic managementinchildren is to initiate treatment with acetaminophen as the primary therapy, followed byNSAIDs,andreservingopioids asalastchoice.

Keywords:Analgetictherapy,Pediatricsurgery,post-operativemanagement.

1.INTRODUCTION

Paininchildrenisidenticaltothatinadultsandcanharmthebody. Anticipating andtreatingpediatricpainiscritical.Anunpleasantexperiencelikepain canaffectallphysiologicalsystems.Paincanbepreciselyquantifiedinchildren utilizingage-specificpainscoringsystems.Analgesicsshouldbeusedearlyandin sufficientamountsto work.A multimodal approachcombiningmilderanalgesicsand localizedblockscancontrolpainandpreventseveresideeffectsfrompotent analgesics.Recentadvancesinanalgesicpharmacologyallowforbroadusewith minimaladverseeffects.Patient-ornurse-controlledanalgesiaandcontinuous regionalnerveblockswithindwellingcatheterscanimprovepediatricpain management.[1]Painalleviationhasphysiologicalbenefits,thereforemonitoringitis becomingakeypostoperativequalitymeasure.Painmanagementaftersurgery aimstorelievediscomfortwithminimalsideeffects.[2,3]

Postoperativepaintherapyiscrucialforhospitalsformanyreasons.Proper therapyaffectspatientcare,hospitalcosts,andcomorbidities.Acutepostoperative painremains a barrier formodernmedicine despite pharmacological and

technologicalimprovements.However,acutepostoperativepainshouldbetreated basedontheintensityofthesurgicalprocedure,theanalgesics,andadequate combinationsthatenhanceanalgesiceffectsratherthansideeffects,aswellas locoregionaltechniquesassociatedwiththesurgicalsite.[4,5]Thisstudyaimsto investigatethemechanismofaction,cellulartargets,andclinicaloutcomeof analgetictherapyinpost-operativepediatricsurgicalpatients.

2.METHODOLOGY

Theliteraturesearchinthisreviewwascarriedoutusing Pubmedand GoogleScholardatabaseswiththreemainkeywords:pediatricsurgery,analgetic therapy,andpost-operativemanagement.Thearticleswereselectedbasedon language,typeofpublication,suitabilityofmethods,casecharacteristics,exposure, andoutcome.Allreferencesthatmatchtheinclusioncriteriaareprocessedusing theMendeley®citationmanager,whereas30articlesareobtainedasreferences. In thisreview,authorsincludethreetypesofanalgeticdrug:Acetaminophen,NSAID, andopioidswiththreeindicatorsofcomparison:Mechanismofaction,cellular targets andtheclinicaloutcomeofthepatient.

3. RESULTSANDDISCUSSION

Acetaminophen

- Mechanismofaction

  Paracetamolasthemostcommonuseacetaminophendrugisafirst-line oral analgesicfor long-termusage.Children'sparacetamoluserequiresspecific attentionandage-appropriatedosage,unlikeadults'.Paracetamolmetabolism determinestoxicity,notablyhepatotoxicity,hencechildren'sdosageisbasedon this.Younger childrenusethesulfation pathwaytoeliminateparacetamol,which ismatureatbirth,whiletheglucuronidationpathwaytakestwoyearstomature. Inhumans,paracetamolismetabolizedintheliverthroughglucuronidation(50-60%),sulfation(25-30%),andoxidation(<10%).Centralfunctionofparacetamol isitsstimulationofdescendingserotoninergicpathways,whichreducepain.In vivotestsonanimalsandhumansvalidatedthisnotion,showingthatthisdrug's centralantinociceptive impact involves the 5-HT3 subtype of serotonin receptors.[6,7]

- Cellulartargets

  Themechanismsofacetaminophen's clinical selectivity remainunknown. TraditionalNSAIDsblockorchangetheactivesiteofcyclo-oxygenase,however acetaminophenmaynot.Twomaintheoriesexist.First,acetaminophenmay preferentiallyblockacentralnervoussystemcyclooxygenaseisoform,maybe thecaninebrain'sputativecyclooxygenase-3.Second,acetaminophenmay impedecyclo-oxygenaseactionbyconvertingitsactiveoxidizedformtoan inactiveformratherthanbindingtoitsactivesite.Thus,lowperoxide concentrationsmakeacetaminopheninhibitionmoreeffective.Thistheory explainsacetaminophen'snerve-specifictherapeuticselectivity.Nerves,which aresensitive to intracellular oxidants, actively minimize oxidation. The inflammatorylocationmayhavehighoxidantlevels,makingacetaminophen's lowering effects ineffective. Acetaminophen preferentially inhibits cyclo-oxygenaseactivityinendothelialcellsbutnotplatelets,andincreasing

intracellularperoxidelevelspreventsitsinhibitoryeffects.[8]

Anotherpossibilityforcellularselectivityinacetaminophenresponseis thatthedrug'smetabolicdestinychangesamongcells,whichcouldaffectits efficacybyforminganactivemetaboliteoracceleratingdruginactivation. Acetaminophenbiotransformationdataisplentifulandsuggestsselectivity. Acetaminophenismetabolizedintheliverbyglucuronidationandsulfate conjugation.Acetaminophenisdeacetylatedtoproducep-aminophenol,a powerfulnephrotoxicant.Substanceofp-aminophenolinhibitsthromboxaneA2 productioninwashedplateletsmorethanacetaminophen,basedonthisand evidencethatitinhibitsPGHSintheratrenalmedulla.Thesefindingsprovidea clearrationalefordeterminingtheextentofacetaminophendeacetylationin relationtocellularselectivity,buttheroleofcell-ortissue-specificdeacetylation inclinicalbehaviorremainstobeexplored.Arecentstudysuggeststhat acetaminophen'sanalgesicqualitiescomefromadownstreammetaboliteofp-aminophenol.Additionalresearchisneededtoprovethatthismetabolic pathwayforacetaminophenisnecessaryforitsanalgesiceffectsandthat humanshavesuchpathways.[9]

- Clinicaloutcome

Acetaminophencandamagetheliverinlargedoses,howeverliver failureriskdependsonhealthandotherfactors.Becauseanintricatesystemof intra-andextracellularmolecularsignalingregulatesAPAP-inducedliverinjury andrecovery,weaimtoquantifytheimportanceofspecificmodulesin determiningtheoutcomeafteranAPAPinsultandofpotentialtargetsfor therapiesthatmitigateadversity.[10]Becauseitinhibitsprostaglandinsynthesis, acetaminophenhasextremelyselectiveanalgesicandantipyreticeffects. Arachidonicacid-derivedPGsarekeymediatorsofinflammation,fever,and discomfort. A practical investigation showed that intraoperative IV acetaminophenwas safeandbeneficialfor postoperativepainfollowingpediatric skinlaserirradiation.Inthatstudy,theacetaminophenIVgrouphadlowerpain levelsthantheplacebogroupupto2hourspostoperatively,exceptfor emergence.[11]

Non-SteroidAntiInflamatoryDrugs(NSAID)

- Mechanismofaction

Non-steroidalanti-inflammatorydrugs(NSAIDs)areutilizedfortheir powerfulanalgesic,anti-inflammatory,andantipyreticproperties.NSAIDswork by inhibiting COX enzyme, which biosynthesizes prostaglandins and thromboxane. Fever,pain,andinflammationaremediatedbyPGs andTXs.The pathophysiologyofmanydiseasesinvolvesinflammation.PGs,coagulation cascade-derivedpeptides,IL-2,IL-6,andTNFareaffectedbyNSAIDs. Arachidonicacid-derivedprostanoidspromoteinflammation.[12,13]

Theimmunesystemisdirectlyactivatedbysurgicalinjurythroughthe bindingofdanger-associatedmolecularpatternstopatternrecognitionreceptors intheinnateimmunesystem.Additionally,theneuroendocrinesystemis indirectlyactivatedthrough the hypothalamic-pituitary-adrenal axis. Upon activation,acascadeofhormones,cytokines,chemokines,andprostanoidsare producedinordertorestorethebody'sinternalbalance,promotetissuehealing,

andcombatinfections.Anti-inflammatorynonsteroidalanti-inflammatorydrugs (NSAIDs)maybebeneficialforthisconditionastheyinhibitthesensitivityof boththeperipheralandcentralnociceptivepathways.Ibuprofen,diclofenac, ketorolac,naproxen,andflurbiprofenwereemployed,howeverCOX-2inhibitors shownagreaterreductioninpostoperativeanalgesicconsumptioncomparedto nonselectiveNSAIDs.[14]

- Cellulartargets

NSAIDsarehighlyeffectiveanalgesicsandareamongthemost commonlypurchasedmedications.Itisnecessarytoinvestigatethemolecular interactionsthatareresponsibleforboththephysiologicalactivityandthe detrimentaleffectsofthesesubstances.Ibuprofen,naproxen,anddiclofenac, which are widely used NSAIDs, have an interaction withdimyristoylphosphatidylserine,aprominentphospholipidfoundineukaryotic cells.Fourier-transforminfraredspectroscopy(FTIR)anddifferentialscanning calorimetry(DSC)areemployedtoobservethechangefromgeltoliquid crystallinephaseoftheacylchains,bothintheabsenceandpresenceofthe NSAID.TheinteractionsbetweenNSAIDsandfunctionalgroupsintheDMPS spectrum,suchastheestercarbonylandphosphatevibrationalbands,are detectedandrecordedusingFourierTransformInfraredSpectroscopy(FTIR)in reflectionmodewithAttenuated Total Reflection (ATR) technique. The thermodynamicsoftheinteractionbetweenNSAID-DMPSliposomesare assessedusingisothermaltitrationcalorimetry(ITC)andFörsterresonance energytransfer(FRET). Thedataindicatethat theNSAIDinteractswith thislipid inaspecificmanner,whileexhibitingdistinctdifferencesinotherparameters. Thisprovidesacomprehensiveunderstandingoftheinteractionprocesses.Our investigationrevealedthatNSAIDssuchasibuprofen,naproxen,anddiclofenac causedthedestabilizationofDMPSbilayers,resultingindetrimentaleffectson theirthermodynamicproperties.Drug-membraneinteractionis influencedby multipleaspects.Hydrationisessentialforthestabilizationofbilayers.The presenceofahydrationshellandthearrangementoflipidscanhaveanimpact oncellmembranes,influencingtheirsemipermeableproperties,therateand efficiencyofcelldevelopment,andtheactivityofenzymeslinkedwiththe membrane.[15]

- Clinicaloutcome

Ibuprofenisthemostextensivelyresearchedandutilizednonsteroidal anti-inflammatorydrug(NSAID)inchildrenfor thetreatmentofsudden pain,and itisthesoleNSAIDauthorizedforuseinchildrenasyoungas6months.Allof thestudiesonibuprofenexaminedadverseevents(AEs)andotherfactors relatedtosafetyandtolerability,suchasnausea,vomiting,drowsiness,and dizziness.[16]Theidealpediatricibuprofendoseis10mg/kgbodyweightevery8 h,withthemaximumsingledoseanddailydosebeing800mgand2400mg, respectively.Severeibuprofentoxicityinchildrenatdoseslessthan100mg/kg byhistorythroughouttreatmentisrare.Morethan400mg/kgbodyweightcan causeseriousorlife-threateningtoxicitiesincludegastrointestinalhemorrhage, thrombocytopenia, pulmonary edema, severe acute kidney failure, and metabolicacidosis.Sincethereisnoantidote,mainsupportivemeasures should beused.[17]

NSAIDshavemanyadvantageanddisadvantageduetotheorgan system.Intheurinarysystem,NSAIDsinhibitkidneyCOX-1andintravascular volume-dependentinducibleCOX-2.WhileCOX-1controlsglomerularfiltration rateandrenalhemodynamics,COX-2controlssaltandwaterexcretion.Inthe nervoussystem,NSAIDsmaydelayAlzheimer's.InhibitingCOX-2disruptsthe β-amyloidcascade,whichsuppressesmemoryandsynapticplasticity.[18] Moreover, NSAIDscanaffect theGIsystembydeterioratingthisprocess.These harmscanbecausedbyPGornon-PGmethods.Agastriclesioncausedby increasedmucosalpermeabilityandmyeloperoxidaseactivityincreasesgastric hypermotility.Inthe cardiovascularsystem,selectiveCOX inhibitorslowerPGI2, whichisessentialforendothelialcellvasodilationandplateletinhibition, increasingtheriskofthrombosis.PGI2andTXA2,avasoconstrictor,can becomeimbalanced,causingplateletaggregationandthrombusdevelopment.[12]

Inthegeneralpopulation,0.3%ofadultsand0.5%ofchildrenhave hypersensitivityreactionstoNSAIDs.Ibuprofenwasthemostcommonly implicatedNSAID(7,6%ofcases).Treatmentdurationanddrugdosesshould befrequentlyassessedandmanufacturerorexpertcommitteemaximumdose limitsandotherguidelinesfollowed.ThemedicalteamshouldstartNSAID medicationwiththelowestage-orweight-baseddosetoimprovesafetyin newbornsandchildren.BecauseNSAIDsareusedbyasignificantnumberof children,hypersensitivityshouldalwaysbeconsideredasadrug-induced adverseeventthatmustbemonitoredandhandled.[19–21]

Opioids

- Mechanismofaction

Opioidsaffecttheafferentandefferentpainpathways.Theyblockpain transmission from primary afferent to ascending neuronesby lowering neurotransmitterrelease.KþandCa2þchannelsplayamajorroleinthese processes,withactivationincreasingKþeffluxandhyperpolarization,while inhibitiondecreasesCa2þinfluxandlimitstransmitterrelease.Second-to-third-ordertransmissionanddescendinginhibitorycontrolactivitiesareenhancedby reducingGABAergicinhibitorytransmission.PlasticityexistsinNOPreceptor andpainprocessing.[22]NOP,MOP(m),KOP(k),andDOP(d)areclassical opioidreceptorsaccordingtoIUPHAR.AllfourG-protein-coupledreceptors haveaseven-transmembranetopology.Insteadofdirectlycommunicatingwith

effectorproteins,G-protein-coupledreceptors(GPCRs)conveythemessage. MOPwithmorphineclosesvoltage-sensitivecalciumchannels(VSCCs), stimulatespotassiumefflux,hyperpolarizescells,andreducescyclicadenosine monophosphate(cAMP)productionbyinhibitingadenylylcyclase.Allfour receptorsubtypespreferentiallycoupletoinhibitoryG-proteins.Thisdecreases neuronal cell excitability, reducing nerve impulse transmission and neurotransmitterrelease.[23]

- Cellulartargets

  Numerousphysiologicalfunctionsdependonopioidreceptors,whichare widelydistributedinthebody.Theseincludecentralandperipheralnervous systempainsignaling,reproduction,growth,breathing,andimmunological response. Physiologically and pathophysiologically, opioid receptors are importantintheGItract.GPCRsaretargetsforaboutone-thirdofFDA-approved blockbuster medications, including analgesics, antihistamines, neuroleptics,andnumerouscardiovasculartherapies.Theopioidreceptorfamily iskeyGPCR.MOP,DOP,andKOPareprototypicalnaloxone-sensitiveopioid receptors.Thisfamilyalsoincludesthenonclassicalnociceptin/orphaninFQ (N/OFQ)receptor.Naloxonedoesnotaffectthisreceptor.Opioidsbindto Gi/Go G-proteins,causingneuronhyperpolarization,closingvoltage-gatedCa2þ channels, and inhibiting adenylyl cyclase to reduce cyclic adenosine monophosphate formation and membrane repolarization. The b-arrestin pathwayinhibitssignaling.Thesecoordinatedcellularactivitiesallowallfamily memberstoproduceanalgesia(anti-nociceptioninnon-humans)tovaried degreesandlocales.G-proteinandindependentb-arrestinpathwayslinkopioid receptorstomitogen-activatedproteinkinasessuchESRPK,p38,andJun Nterminalkinase.Allmembersofthefamilycanprovideanalgesia,butMOP receptoragonistsarethemainstayintheclinic,withsomedevelopinginstances addressednext.Thelistincludesmorphine,fentanyl,andoxycodone.Opioids havemanysideeffects,includingventilatorydepression,nauseaandvomiting, constipation,tolerance,anddependency.Tolerancecausesdoseescalation (particularlyinpalliativecare)anddependence,whichisassociatedto prematuredeathandcrimeglobally.[24,25]

- Clinicaloutcome

  Studies suggest non-opioid medications are equally effective in controllingpost-operativepainafterpediatricherniorrhaphycomparedtoopioid medications.Routineopioidadministrationdoesnotappeartopositivelyaffect postoperativepainmanagementinthispopulationandisassociatedwitha higherrateofmedicationrelatedsideeffects.Moststudysuggeststhatopioid prescriptionsaremorelikelytocauseharmintheformofworsenednauseaand vomitingthanprovideimprovedpaincontrol.[26]

  Dixitetal.2022reportedthatsurgeryasariskfactorforopioiduse, persistence,andmisuseinchildren.Intheexperiment,849(63.1%)of1344 pediatricambulatorysurgerypatients responded. Surveyrespondentswere60% male,55%2–12-year-olds,and90%ASA1or2patients.Theaverage proceduretook1h.32.4%of275dischargedpatientsreceivedopioids.164 (59.6%)postoperativeopioidusersdidnotusethemonPOD1.Orthopedicand

plasticsurgeryhad28–29%wastedopioidprescribing,whiledentistryand ophthalmologyhad3–4%.Neurosurgicalpatientsreceived55%opioidsandall usedthemonPOD1.Obstetrics,dentalandmaxillofacialsurgery,orthopedic surgery,andplasticsurgerydischargedatleast60%ofpatientsonopioids,with 33–42%notusingopioidsonPOD1.Operativeandpatient-specificopioiddays andOMEsperkilogramdifferedsubstantially.Somechildrenhad3-to7-day opioidprescriptionsaftertonsillectomyandadenoidectomy,whileonereceived >15 days.Some patients received opioids for10daysafterorchiopexy. Mostgot 2–4days.Thesefindingsrepresentoralmorphineequivalentsperkilogram. Olderpatients,thosewithprivateinsurance,thosewithlongersurgeries,and thosefurthestfromthehospitalwereprescribedmoreopioids.Medicalopioid exposuremakesadolescentsmorelikelytouserecreationally,share,and developdrugdependenceandmisuse.Opioidexposureandchronicusageare linkedtosurgery,with6-10%ofopioid-naïvepersonsconsumingopioidsfor beyond3monthsorevenayearaftersurgery.Aftercholecystectomy, arthroscopickneesurgery,colectomy,andwisdomtoothextraction,5%of pediatricpatientsfillopioidprescriptions2–6monthslater.[27]

Otheropioid-relatedissues,suchasopioidusedisorder,stemfrom opioidusage.In2016,thereareabout153,000childrenin12–17-year-oldsin theUSreportedopioidusedisorder.Mostopioidusedisordercases(99%) involvedprescriptionopioids,withheroinaccountingfor1%.Opioidsarethe leadingcauseofseriousinjuryordeathinchildren,andaccidentalopioid overdosesintheUSdoubledfrom1999to2008.In2008,opioid-related accidentaldeathswere0.1per100,000forchildren0–14and3.7per100,000 forteenagers15–18.After2008,opioid-relatedadolescentmortalitydroppedto 2.0 per 100,000in2011and 2.5per100,000in2015.[28–30]

4.CONCLUSION

Thisbriefreviewshowedthatallresearcherandclinicianagreedthatpost operativeanalgesiamanagementforchildrenstillmustbestartedbyusing acetaminophenasinitialteraphy,then NSAIDandOpioidsasthelastchoice.

CONSENT

Nonetodeclare.

ETHICALAPPROVAL

Nonetodeclare.

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